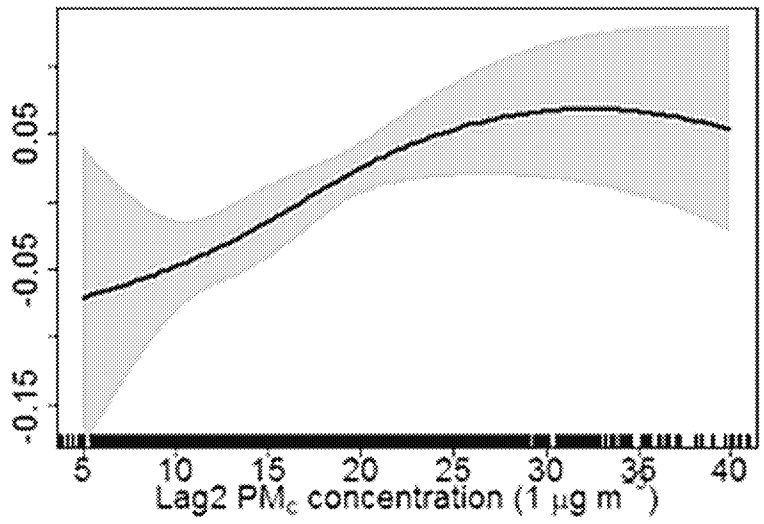


Source: Permission pending, Zhao et al. (2016).

Figure 5-41 Concentration-response relationship between short-term $PM_{10-2.5}$ exposure and asthma emergency department (ED) visits at lag 2 for a natural spline model with three degrees of freedom (df) for Dongguan, China.

5.3.2.2 Respiratory Symptoms and Medication Use

As discussed in Section 5.1.2.2, uncontrollable respiratory symptoms can lead people with asthma to seek medical care. Thus, studies examining the relation between $PM_{10-2.5}$ and increases in asthma symptoms may provide support for the observed increases in asthma hospital admissions and ED visits in children, as discussed in Section 5.3.2.1. A single U.S. study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined respiratory symptoms in people with asthma. Mar et al. (2004) reported $PM_{10-2.5}$-related increases across a number of self-reported symptoms in children, including wheeze, shortness of breath, cough, increased sputum, and runny nose. The authors did not observe associations in healthy adults.

Evidence from a limited number of recent panel studies further supports an association between $PM_{10-2.5}$ and respiratory symptoms in asthmatic children. Wheeze was associated with $PM_{10-2.5}$ in a panel study of children in Fresno, CA (Mann et al., 2010). The reported association was observed with 3-day lag $PM_{10-2.5}$ concentrations from a single monitor (OR: 1.07 [95% CI: 1.01, 1.14]), but the authors noted that the association was relatively stable across lags. Associations are also supported with $PM_{10-2.5}$ measured on the rooftops of two schools in El Paso, TX (Zora et al., 2013). 4-day average $PM_{10-2.5}$ concentrations measured outside of the schools were associated with poorer asthma control scores, which reflect symptoms and activity levels. The two schools included in the study differed in nearby traffic levels but varied similarly in outdoor $PM_{2.5}$ concentration over time (Section 3.4.3.1). Prieto-Parra et al. (2017) also observed associations between 7-day average coarse PM and cough and wheeze in Santiago,

Chile. Notably, the authors reported that $PM_{10-2.5}$ was associated with decreased bronchodilator use (Prieto-Parra et al., 2017).

5.3.2.3 Lung Function

There were no epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that examined the association between $PM_{10-2.5}$ and lung function in populations with asthma. One recent study observed a decrease in FEV_1 in children associated with 4-day average $PM_{10-2.5}$ concentrations measured outside of two El Paso schools (Greenwald et al., 2013).

A single controlled human exposure study evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the effects of short-term exposure to $PM_{10-2.5}$ on lung function. Jr et al. (2004) did not observe significant decrements in pulmonary function in human subjects with asthma exposed to $PM_{10-2.5}$. Recently, Alexis et al. (2014) conducted a proof-of-concept study to confirm the assumption that $PM_{10-2.5}$, like other pollutants, can initiate deleterious responses in individuals with asthma at concentrations not observed in healthy individuals. This assumption is based on people with asthma having elevated levels of pre-existing inflammation and altered innate immune function compared to healthy individuals, which may enhance their susceptibility to $PM_{2.5-10}$-induced health effects. Alexis et al. (2014) exposed individuals with mild asthma for 2 hours to either $PM_{10-2.5}$ CAPs or filtered air collected from ambient air in Chapel Hill, NC (see Table 5-30 for study details). No measure of lung function (i.e., FEV_1 and FVC) was affected in $PM_{10-2.5}$-exposed subjects.

Table 5-30 Study-specific details from a controlled human exposure study of short-term $PM_{10-2.5}$ exposure and lung function in populations with asthma.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Alexis et al. (2014)	Single-blind cross-over	Mild to moderate individuals with asthma; n = 10; sex not stated (18–45 yr)	86.9 ± 17.4 μg/m^3 $PM_{10-2.5}$ for 2 hr with intermittent exercise (15 min of rest followed by 15 min of exercise on recumbent bicycle). Comparison group was clean air; a wash-out period of at least 4 weeks was used between exposures.	BAL and BW (24-hr post-exposure): Differential leukocyte counts, IL-6, IL-8, IL-1β, TNF-α, flow-cytometry to identify cell surface phenotypes Spirometry (24-hour post-exposure): FEV_1, FVC

BAL = bronchoalveolar lavage; BW = bronchial wash; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-1β = interleukin 1β; TNFα = tumor necrosis factor α.

5.3.2.4 Subclinical Effects Underlying Asthma Exacerbation

5.3.2.4.1 Epidemiologic Studies

No epidemiologic studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) examined the association between short-term exposure to $PM_{10-2.5}$ and subclinical respiratory effects in populations with asthma. Recent panel studies of schoolchildren in El Paso provide inconsistent evidence of an association between $PM_{10-2.5}$ and eNO, an indicator of pulmonary inflammation. Among children at four schools in the neighboring cities of El Paso, TX and Ciudad Juarez, Mexico, eNO was associated with 48-hour average outdoor $PM_{10-2.5}$ (Sarnat et al., 2012). While Sarnat et al. (2012) reported an association between 2-day average outdoor $PM_{10-2.5}$ concentrations and eNO in El Paso, a follow-up study of children in the same schools in El Paso observed a null association with 4-day average outdoor $PM_{10-2.5}$ concentrations (Greenwald et al., 2013). The associations observed by Sarnat et al. (2012) appear to have been driven largely by results from children in one school (Ciudad Juarez) with the highest mean $PM_{10-2.5}$ concentrations.

5.3.2.4.2 Controlled Human Exposure Studies

A single study evaluated in the 2009 PM ISA (U.S. EPA, 2009) investigated whether short-term exposure to $PM_{10-2.5}$ was associated with subclinical outcomes in individuals with asthma. Jr et al. (2004) did not observe changes in lung function or markers of airway inflammation in individuals with asthma who were exposed to $PM_{10-2.5}$. Recently, Alexis et al. (2014) exposed individuals with mild asthma for 2 hours to either $PM_{10-2.5}$ CAPs or filtered air collected from ambient air in Chapel Hill, NC. Differential leukocyte numbers and cell surface markers on recovered leukocytes were examined (see Table 5-31 for study details). The authors reported an increase in BW polymorphonuclear neutrophil concentration (8 vs. 13%, $p < 0.05$) and that this effect was different from effects observed when healthy subjects were exposed to a similar concentration of course PM (Graff et al., 2009). Levels of IL-1β and IL-8 were also elevated in both BW and bronchoalveolar lavage (BAL) samples ($p < 0.05$). Short-term exposure to $PM_{10-2.5}$ CAPs also induced decreased expression of innate immune (CD11b/CR3, CD64/FcγRI) and antigen presentation (CD40, CD86/B7.2) cell surface receptors, and increased expression of inflammatory cell surface receptors (CD16/FcγRIII) and the low-affinity IgE receptor (CD23). The up-regulation of the CD23/IgE receptor reported by Alexis et al. (2014) suggests an asthma-specific pathway induced by $PM_{10-2.5}$, a pathway not typically observed with other xenobiotics, such as O_3 or endotoxin. In summary, the observations reported by Alexis et al. (2014), namely that significant $PM_{10-2.5}$ CAPs-induced pulmonary inflammation, altered innate host defense response, and potentially enhanced IgE signaling, supports the hypothesis that individuals with asthma have greater sensitivity to the inflammatory and immune modifying effects of short-term $PM_{10-2.5}$ CAPs exposure. Furthermore, short-term $PM_{10-2.5}$ CAPs exposure may increase the airway responsiveness of individuals with allergic asthma to inhaled allergens and thereby enhancing the overall risk of asthma exacerbation.

Table 5-31 Study-specific details from a controlled human exposure study of short-term $PM_{10-2.5}$ exposure and subclinical effects underlying asthma.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Alexis et al. (2014)	Single-blind cross-over	Individuals with mild to moderate asthma; n = 10; sex not stated (18–45 yr)	86.9 ± 17.4 ug/m^3 $PM_{10-2.5}$ for 2 hr with intermittent exercise (15 min of rest followed by 15 min of exercise on recumbent bicycle). Comparison group was clean air; a wash-out period of at least 4 weeks was used between exposures	BAL and BW (24-hr post-exposure): Differential leukocyte counts, IL-6, IL-8, IL-1β, TNF-α, flow-cytometry to identify cell surface phenotypes Spirometry (24-hr post-exposure): FEV_1, FVC

BAL = bronchoalveolar lavage; BW = bronchial wash; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-1β = interleukin 1β; TNFα = tumor necrosis factor α.

5.3.2.4.3 Animal Toxicological Studies

There were no studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) that investigated the effects of short-term exposure to $PM_{10-2.5}$ in animal models of allergic airway disease, which share phenotypic features with asthma (see Section 5.1.2.4). Inhalation exposure of rodents to $PM_{10-2.5}$ is technically difficult since rodents are obligatory nasal breathers. A group of recent studies involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-nasal instillation, subcutaneous injection) provide biological plausibility for a role of $PM_{10-2.5}$ in enhancing allergic responses (Kurai et al., 2016; McGee et al., 2015; Kurai et al., 2014; He et al., 2012; Alberg et al., 2009).

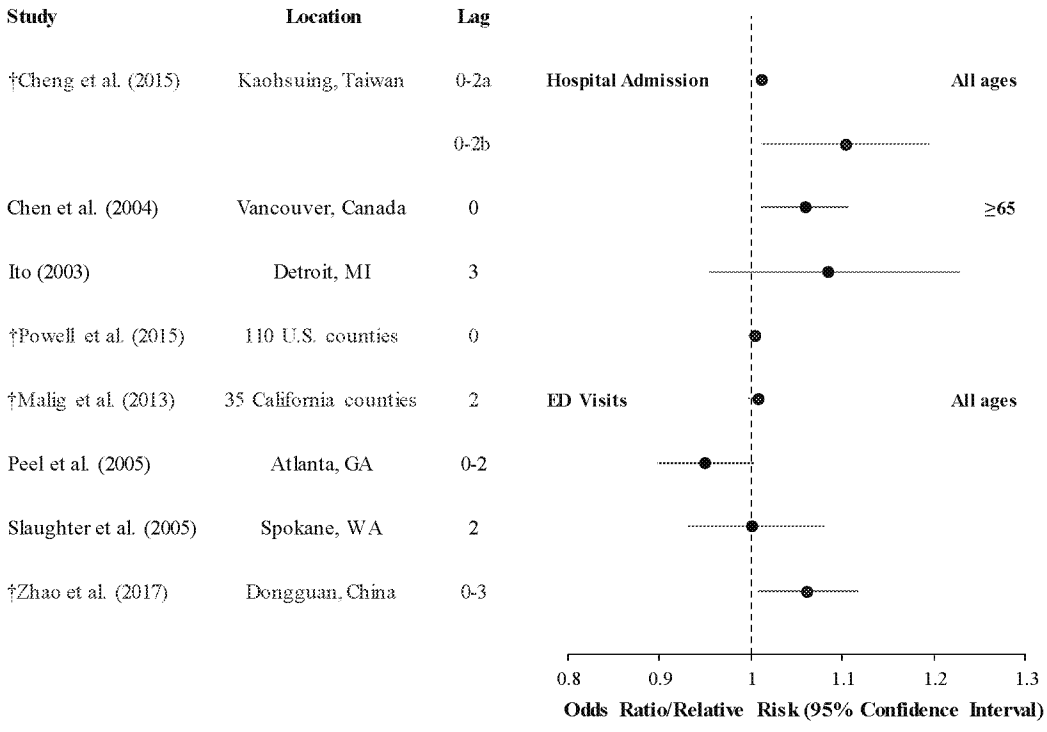
5.3.2.5 Summary of Asthma Exacerbation

Recent epidemiologic findings more consistently link $PM_{10-2.5}$ to asthma exacerbation than studies reported in the 2009 PM ISA. Studies of asthma hospital admission and ED visits include children older than 5 years. These findings are supported by epidemiologic studies observing respiratory symptoms in children, but coherence does not clearly extend to other asthma-related effects since associations were not observed between short-term $PM_{10-2.5}$ exposure and lung function and epidemiologic evidence for pulmonary inflammation was inconsistent. There is limited evidence that

associations remain robust in models with gaseous pollutants and $PM_{2.5}$. An uncertainty related to $PM_{10-2.5}$ measurements is how adequately the spatiotemporal variability is represented given that measurements are mainly based on subtraction of $PM_{2.5}$ from PM_{10} at different locations. Evidence for an independent effect of short-term $PM_{10-2.5}$ exposure was provided by a controlled human exposure study showing effects on inflammation and the immune system.

5.3.3 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Among the few epidemiologic studies available for the 2009 PM ISA (U.S. EPA, 2009), short-term exposure to $PM_{10-2.5}$ were inconsistently associated with hospital admissions for COPD and lung function changes in adults with COPD. Recent studies are relatively limited in number but improve on previous studies with residential exposure assessment, additional outcomes, and analysis of potential copollutant confounding (Figure 5-42 and Table 5-32). Recent studies show associations of $PM_{10-2.5}$ with COPD hospital admissions, ED visits, respiratory symptoms, and pulmonary inflammation. However, the evidence overall is inconsistent across several U.S. and Canadian cities, for older adults, and for direct $PM_{10-2.5}$ measurements.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-42 Summary of associations between short-term $PM_{10-2.5}$ exposures and chronic obstructive pulmonary disease (COPD) hospital admissions and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations.

Table 5-32 Epidemiologic studies of $PM_{10-2.5}$ and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration ($\mu g/m^3$)[a]	Upper Percentile Concentrations ($\mu g/m^3$)[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
Direct $PM_{10-2.5}$ measurement by a dichotomous monitor					
Peel et al. (2005) Atlanta, GA 1998–2000	One monitor (Van Loy et al., 2000)	ED visits All ages	9.7 (4.7)	90th: 16.2	No copollutants examined
Ito (2003) Detroit, MI 1992–1994	One monitor	Hospital admissions Older adults, age NR	13 (SD NR)	75th: 17 95th: 28	Correlation (r) = 0.42 $PM_{2.5}$, 0.77 PM_{10} No copollutant model
†Sinclair et al. (2010) Atlanta, GA 1998–2002	One monitor	Outpatient visits for acute respiratory illness	9.6 (5.4)	NR	No copollutants examined
Difference of PM_{10} and $PM_{2.5}$ measurements					
†Malig et al. (2013) 35 California counties 2005–2008	Difference of collocated PM_{10} and $PM_{2.5}$ concentration, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	ED visits All ages	5.6 (3.1) to 34.4 (25.6)	NR	Correlation (r) = 0.31 $PM_{2.5}$, 0.30 O_3, 0.14 CO Copollutant models examined: $PM_{2.5}$
Chen et al. (2004) Vancouver, Canada 1995–1999	Concentrations averaged for 13 census divisions; authors did not state if PM_{10} and $PM_{2.5}$ monitors were collocated.	Hospital admissions Older adults ≥65 yr	5.6 (3.6)	75th: 7.3 Max: 24.6	Copollutant correlations NR Copollutant models examined: $PM_{2.5}$, O_3, NO_2, CO

Table 5-32 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration ($\mu g/m^3$)[a]	Upper Percentile Concentrations ($\mu g/m^3$)[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
†Zhao et al. (2016) Dongguan, China 2013–2015	Difference of collocated PM_{10} and $PM_{2.5}$ concentration, averaged over five monitoring sites.	Hospital clinic visits All ages	18.6 (9.2)	75th: 22.6 Max: 96.4	Correlation (r) = 0.42 O_3, 0.58 SO_2, 0.60 NO_2 Copollutant models examined: O_3, SO_2. NO_2
†Cheng et al. (2015) Kaohsiung, Taiwan 2006–2010	Difference of PM_{10} (β ray absorption) and $PM_{2.5}$ (TEOM) concentrations collocated, averaged across six monitoring sites.	Hospital admissions All ages	Median (IQR) 24.8 (24.4)	75th: 30.8 Max: 490	Correlation (r) = 0.64 $PM_{2.5}$, 0.89 PM_{10}, 0.24 O_3, 0.53 NO_2, 0.47 CO, 0.19 SO_2 Copollutant models examined: O_3, NO_2, CO, or SO_2
Slaughter et al. (2005) Spokane, WA 1995–1999	$PM_{10-2.5}$ concentration estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors at one site.	ED visits All ages	NR	NR	Correlation (r) = 0.31 $PM_{2.5}$, 0.94 PM_{10} No copollutant model
†Powell et al. (2015) 110 U.S. counties 1999–2010	Difference of PM_{10} and $PM_{2.5}$ concentrations collocated at one monitoring site for each county.	Hospital admissions Older adults ≥65 yr	Median (IQR) 12.78 (3.06)	75th: 15.84	No copollutants examined

CO = carbon monoxide, ED = emergency department, IQR = interquartile range, max = maximum, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤10 μm and >2.5 μm, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 μm, PM_{10} = particulate matter with a nominal mean aerodynamic diameter ≤10 μm, r = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide.

[a]All data are for 24-h average.

†Studies published since the 2009 PM ISA.

1

5.3.3.1 Hospital Admissions and Emergency Department (ED) Visits

The body of literature reviewed in the 2009 PM ISA (U.S. EPA, 2009) that examined the association between short-term $PM_{10-2.5}$ exposure and hospital admissions for COPD was small and consisted of single-city studies conducted in the U.S. and Canada. Across studies, there was inconsistent evidence of an association, with the strongest evidence for hospital admissions in adults over the age of 65 years. An initial assessment of the potential confounding effects of copollutants provided some evidence that COPD associations may be attenuated in models with NO_2. Similarly, an international single-city study reported an association between ED visits for COPD and asthma combined and $PM_{10-2.5}$, but the positive association was attenuated after adjustment for $PM_{2.5}$, NO_2 and CO. Similar to the 2009 PM ISA, the evidence base remains limited when examining the association between short-term $PM_{10-2.5}$ exposure and hospital admissions for COPD, but provides some additional evidence for a positive association (see Figure 5-42).

5.3.3.1.1 Hospital Admissions

In a study of 110 U.S. counties, Powell et al. (2015) assessed the relationship between $PM_{10-2.5}$ and COPD-related hospital admissions among residents older than 65 years of age. The authors reported a positive, but imprecise association with COPD hospital admissions in single pollutant models (0.31% [95% PI: −0.39, 1.01]) and copollutant models with same-day $PM_{2.5}$ (0.19% [95% PI: −0.54, 0.92]). COPD-related admissions were also not associated with short-term $PM_{10-2.5}$ exposures occurring during a 1−3-day lag (which would be indicative of a more delayed response) in either single pollutant or copollutant models. Moreover, Cheng et al. (2015) assessed the relationship between $PM_{10-2.5}$ and COPD-related hospital admissions in a case-crossover study in Kaohsuing, Taiwan. This study observed an increase in hospital admissions of 1.02% (95% CI: 1.01,1.03).

5.3.3.1.2 Emergency Department (ED) Visits

In a multicity study conducted in 35 California counties, Malig et al. (2013) examined the association between short-term $PM_{10-2.5}$ exposures and respiratory ED visits, including COPD visits. The authors reported positive associations between $PM_{10-2.5}$ and COPD ED visits at lag 2 days (0.67% [95% CI: −0.04, 1.38]). In a copollutant model with $PM_{2.5}$, the association was stronger (1.48%) and more precise (95% CI: 0.40, 2.56) [results presented in Figure 5-6 and supplemental data, (Malig et al., 2013)]. The COPD relationship at lag 2 remained elevated for those living closer to the monitor (within 10 km vs. 10−20 km), but it was not present among those farther away indicating potential exposure measurement error based on distance to monitor (Section 3.4.2.2).

5.3.3.2 Other Epidemiologic Studies

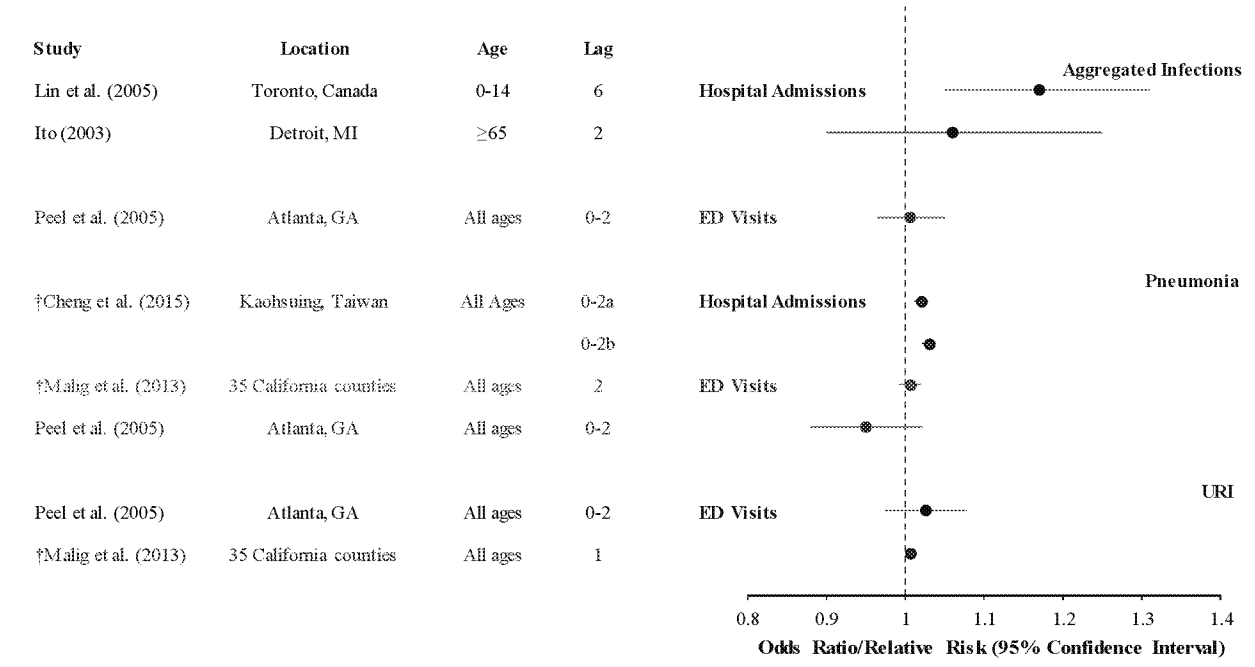
As discussed in the 2009 PM ISA (U.S. EPA, 2009), a limited number of previously evaluated studies provide contrasting evidence of an association between coarse PM and lung function changes in adults with COPD. Associations were not observed for $PM_{10-2.5}$ calculated from residential outdoor PM_{10} and $PM_{2.5}$ in Seattle (Trenga et al., 2006). Conversely, $PM_{10-2.5}$ exposure (24-hour average, lag 0) was associated with a decrease in FEV_1 in adults in Vancouver, Canada (Ebelt et al., 2005). $PM_{10-2.5}$ was calculated by estimating the ambient fractions of $PM_{2.5}$ and PM_{10} measured from personal monitors and subtracting $PM_{2.5}$ from PM_{10}. The $PM_{10-2.5}$ concentrations examined in Ebelt et al. (2005) were lower (mean = 2. $\mu g/m^3$) than those examined for COPD hospital admissions and ED visits (Table 5-9). Neither study examined other pollutants, so it is not clear whether the results reflect an independent association for $PM_{10-2.5}$. There are no recent studies available for review that examine the association between $PM_{10-2.5}$ and indicators of COPD exacerbation.

5.3.3.3 Summary of Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Overall, the body of literature that examined the association between $PM_{10-2.5}$ and hospital admissions and ED visits for COPD is limited. Studies reported in the 2009 ISA (U.S. EPA, 2009) provided inconsistent evidence. Of the recent studies, there is some evidence of a positive association between short-term $PM_{10-2.5}$ exposure and COPD hospital admissions and ED visits, but evidence for other indicators of COPD exacerbation is inconsistent. In addition, there is a relative lack of information on potential copollutant confounding and the potential implications of exposure measurement error due to the different methods employed across studies to estimate $PM_{10-2.5}$ concentrations.

5.3.4 Respiratory Infection

The respiratory tract is protected from exogenous pathogens and particles through various lung host defense mechanisms that include mucociliary clearance, particle transport and detoxification by alveolar macrophages, and innate and adaptive immunity. Impairment of these defense mechanisms can increase the risk of respiratory infection. Previous epidemiologic studies consistently observed associations between short-term $PM_{10-2.5}$ exposure and hospital admissions, ED visits, or physician visits for aggregated respiratory infections or URI, but not pneumonia. In contrast, the few recent epidemiologic studies indicate associations with pneumonia, but not aggregated respiratory infections (Figure 5-43). The 2009 PM ISA (U.S. EPA, 2009) did not report any experimental studies of altered susceptibility to infectious agents following short-term exposure to $PM_{10-2.5}$ and no studies have become available since that time.



Note: †Studies published since the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-43 Summary of associations between short-term $PM_{10-2.5}$ exposures and respiratory infection hospital admissions and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations.

5.3.4.1 Hospital Admissions and Emergency Department (ED) Visits

Although the body of literature was small, the few studies evaluated in the 2009 PM ISA reported inconsistent evidence of an association between $PM_{10-2.5}$ and hospital admissions and ED visits for respiratory infections. Some studies observed associations of respiratory infections with $PM_{10-2.5}$ among subjects younger than 15 years old, and others reported associations between $PM_{10-2.5}$ and outpatient visits for lower respiratory tract infections. The recent literature adds to the evidence base and provides some support for an association between short-term $PM_{10-2.5}$ exposure and hospital admissions/ED visits for pneumonia and respiratory infections considered in aggregate (see Figure 5-43). For each of the studies evaluated in this section, Table 5-33 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study.

In 110 U.S. counties Powell et al. (2015) reported a positive, but uncertain, association between short-term $PM_{10-2.5}$ exposure and respiratory infection hospital admissions among residents older than

65 years in single pollutant models (0.07% [95% PI: −0.46, 0.61]; lag 0). This association was attenuated in a copollutant model with $PM_{2.5}$ (−0.02% [95% PI: −0.59, 0.55]; lag 0). Respiratory infection-related admissions were also not associated with $PM_{10-2.5}$ exposures occurring 1−3 days prior to admission in either single pollutant or copollutant models. Cheng et al. (2015) assessed the relationship between $PM_{10-2.5}$ and pneumonia-related hospital admissions among residents older than 65 years of age in a case-crossover study in Kaohsuing, Taiwan between 2006−2010. This study observed a small positive association, with an increase in hospital admissions of 1.02% (95% CI: 1.01, 1.03) per 10-$\mu g/m^3$ increase in $PM_{10-2.5}$. This association was consistent after model adjustment for SO_2, NO_2, CO, and O_3 and was slightly stronger on colder days below 25°C (1.03% [95% CI: 1.02, 1.04]).

In a multicity study conducted in 35 California counties, Malig et al. (2013) reported no association between short-term $PM_{10-2.5}$ exposures at single-day lags 0−2 days and ED visits due to acute respiratory infection [RR 1.007, 95% CI: 1, 1.01]. This study also reported a very weak association between short-term $PM_{10-2.5}$ exposures at single-day lags 0−2 days for pneumonia visits RR 1.006 [95% CI: 0.99, 1.02].

Table 5-33 Epidemiologic studies of $PM_{10-2.5}$ and respiratory infections.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
Direct $PM_{10-2.5}$ measurement by a dichotomous monitor					
Peel et al. (2005) Atlanta, GA 1998–2000	One monitor	ED visits URI, pneumonia All ages	9.7 (4.7)	90th: 16.2	No copollutant model Copollutant correlations NR
Sinclair et al. (2010) Atlanta, GA 1998–2002	One monitor	Physician visits URI, LRI All ages	Aug 1998–Aug 2000: 9.7 (4.7) Sep 2000–Dec 2002: 9.6 (5.4)	NR	Correlation (r) = 0.43 CO warm season, 0.50 NO_2 cold season No copollutant model
Ito (2003) Detroit, MI 1992–1994	One monitor	Hospital admissions Type of infection NR Older adults	13 (SD NR)	75th: 17 95th: 28	Correlation (r) = 0.42 $PM_{2.5}$, 0.77 PM_{10} No copollutant model
Difference of PM_{10} and $PM_{2.5}$ measurements					
†Malig et al. (2013) 35 California counties 2005–2008	Nearest monitor Within 25 km of population-weighted zip code centroid. Difference of collocated PM_{10} and $PM_{2.5}$ concentration, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	ED visits URI, pneumonia All ages	5.6 (3.1) to 34.4 (25.6)	NR	Correlation (r) = 0.31 $PM_{2.5}$, 0.30 O_3, 0.14 CO

Table 5-33 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory infections.

Study	Exposure Assessment	Outcome Assessment	Mean (SD) Concentration µg/m³[a]	Upper Percentile Concentrations µg/m³[a]	$PM_{10-2.5}$ Copollutant Model Results and Correlations
†Cheng et al. (2015) Kaohshing, Taiwan 2006–2010	Difference of PM_{10} (β ray absorption) and $PM_{2.5}$ (TEOM) concentrations collocated, averaged across six monitoring sites.	Hospital admissions Pneumonia All ages	Median (IQR) 24.8 (24.4)	75th: 30.8 Max: 490	Correlation (r) = 0.64 $PM_{2.5}$, 0.89 PM_{10}, 0.24 O_3, 0.53 NO_2, 0.47 CO, 0.19 SO_2
Lin et al. (2005) Toronto, Canada 1998–2001	Difference of average PM_{10} (β ray absorption) and average $PM_{2.5}$ (TEOM) concentrations across four monitoring sites.	Hospital admissions URI + pneumonia Children <15 yr	10.9 (5.4)	75th: 13.5 Max: 45	Correlation (r) = 0.33 $PM_{2.5}$, 0.76 PM_{10}, 0.30 O_3, 0.40 NO_2, 0.06 CO, 0.29 SO_2 No copollutant model

CO = carbon monoxide, ED = emergency department, IQR = interquartile range, max = maximum, LRI = lower respiratory infection, NO_2 = nitrogen dioxide, NR = not reported, O_3 = ozone, $PM_{10-2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤10 µm and > 2.5 µm, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, PM_{10} = particulate matter with a nominal mean aerodynamic diameter ≤10 µm, r = correlation coefficient, SD = standard deviation, SO_2 = sulfur dioxide, URI = upper respiratory infection.

[a]All data are for 24-h average unless otherwise specified.

†Studies published since the 2009 PM ISA.

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5.3.4.2 Outpatient and Physician Visit Studies

In Atlanta, GA, Sinclair et al. (2010) compared air pollutant concentrations and relationships for acute respiratory visits for the 25-month time-period examined in a previous study (August 1998–August 2000) and an additional 28-month time-period of available data from the Atlanta Aerosol Research Inhalation Epidemiology Study (ARIES) (September 2000–December 2002). Across the two time periods, $PM_{10-2.5}$ mass concentrations (measured from ARIES) were essentially stable with only a 3% difference between the two study periods (9.6 $\mu g/m^3$ overall average). Unlike $PM_{2.5}$ mass, $PM_{10-2.5}$ mass did not change significantly across warm or cold seasons. A comparison of the two time periods indicated that associations for $PM_{10-2.5}$ tended to be larger in the earlier 25-month period compared to the later 28-month period. Associations with URI for lag 3–5 in the 25-month time period represented the highest finding (4.2% [95% CI: 0.75, 7.8]). For LRI in the 25-month period, associations were positive for all lags, with the largest for lag 3–5 (13.2% [95% CI: 3.2, 24.4]). As noted in Section 5.1.2.1, several factors may dictate whether an individual visits the doctor or a hospital, making it difficult to readily compare results between studies focusing on physician visits versus hospital admissions and ED visits.

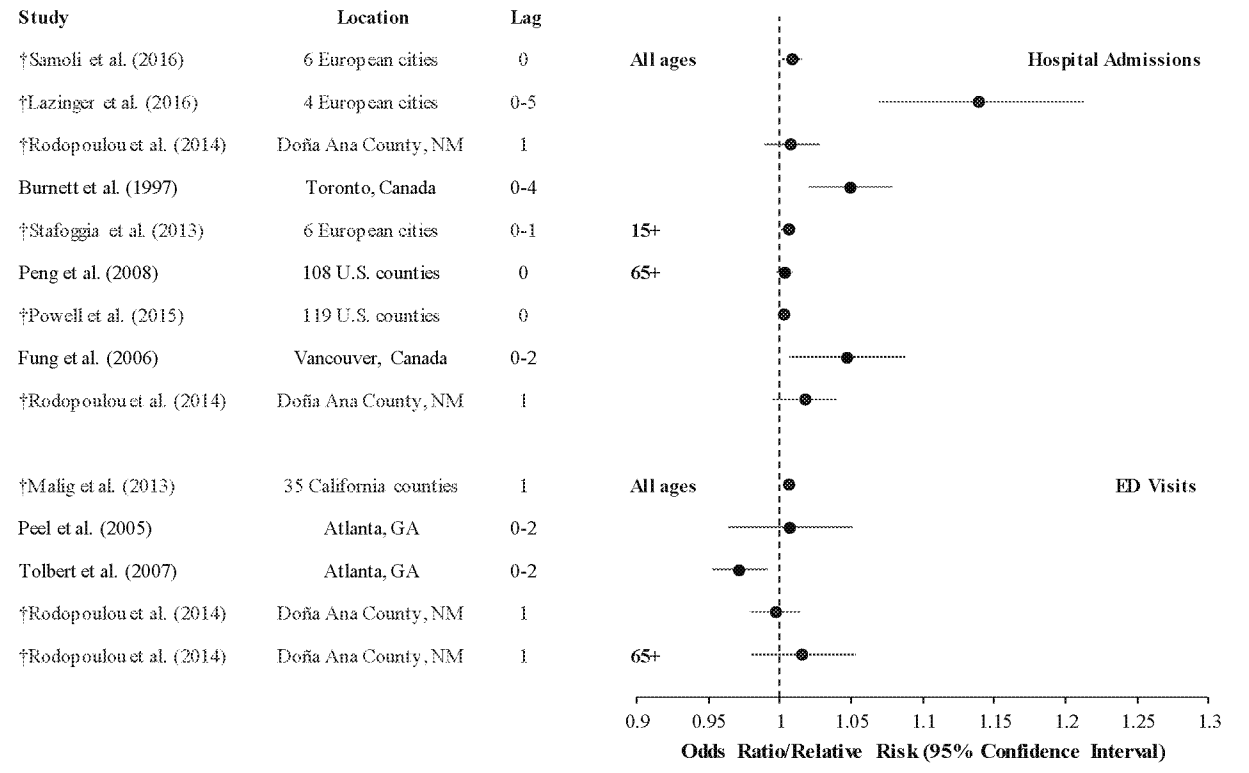
5.3.4.3 Summary of Respiratory Infection

The body of literature that examined the association between $PM_{10-2.5}$ and hospital admissions and ED visits for respiratory infection hospital admissions expanded since the 2009 PM ISA (U.S. EPA, 2009), but remains limited. Previous studies reported associations between $PM_{10-2.5}$ and both acute respiratory infection and a combination of respiratory infection, but not pneumonia. Recent studies are generally indicative of associations for both acute respiratory infection and pneumonia, but not the combination of respiratory infections. A multicity study conducted in the U.S. and several single-city studies in the U.S. and internationally report positive associations between $PM_{10-2.5}$ and hospital admissions/ED visits for pneumonia or acute respiratory infection. Despite some inconsistency between previous and recent findings, the evidence overall is supportive of a link between short-term $PM_{10-2.5}$ exposure and respiratory infection. However, previous and recent findings have similar uncertainties in exposure measurement error in $PM_{10-2.5}$ concentrations, particularly when PM_{10} and $PM_{2.5}$ concentrations that were not collocated were differenced to estimate $PM_{10-2.5}$ concentrations. Previous and recent findings also have uncertainties in limited examination of copollutant confounding and limited information from experimental studies to assess biological plausibility.

5.3.5 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term $PM_{10-2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases was limited to a rather small number of studies. Across hospital admissions studies, there was evidence of positive associations that varied in terms of the magnitude and precision of the estimates, while the evidence for ED visits was inconsistent. Of the studies evaluated in the 2009 PM ISA, the majority consisted of single-city studies, and different approaches were used to estimate ambient $PM_{10-2.5}$ concentrations. Across studies, there was limited to no information on potential copollutant confounding or other assessments of the relationship between short-term $PM_{10-2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases, such as model specification, lag structure of associations, or the C-R relationship.

Recent multi- and single-city studies that examine short-term $PM_{10-2.5}$ exposure and hospital admissions and ED visits for respiratory-related diseases add to the body of evidence detailed in the 2009 PM ISA (U.S. EPA, 2009). Consistent with the studies evaluated in the 2009 PM ISA, recent hospital admissions studies provide evidence of positive associations that are similar in magnitude and precision, while recent ED visits studies provide inconsistent evidence of an association (Figure 5-44). Similar to the studies evaluated in Section 5.1.6, the studies that examined combinations of respiratory-related diseases encompassed all respiratory-related diseases or only a subset, which can complicate the interpretation of results across studies. As described in preceding sections, the evidence for association with $PM_{10-2.5}$ is more consistent for asthma (Section 5.3.1) than for COPD (Section 5.3.2) or for respiratory infection (Section 5.3.4). For each of the studies evaluated in this section, Table 5-34 (summary table of studies) presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each study. Other recent studies of hospital admissions and ED visits for respiratory-related diseases that did not address uncertainties and limitations in the evidence previously identified are not the focus of this evaluation. Additionally, many of these other studies were conducted in small single cities, encompassed a short study duration, or had insufficient sample size. The full list of these other studies can be found in HERO: https://hero.epa.gov/hero/particulate-matter.



Note: †Studies published since the completion of the 2009 PM ISA. Black text = U.S. and Canadian studies included in the 2009 PM ISA. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-44 Summary of associations from studies of short-term $PM_{10-2.5}$ exposures and respiratory-related hospital admissions and emergency department (ED) visits for a 10 µg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations.

Table 5-34 Epidemiologic studies of $PM_{10-2.5}$ and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Hospital admissions					
Peng et al. (2008) 108 U.S. counties 1999–2005 ≥65 yr	Average across sites in a county $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	464–466, 480–487; 490–492	9.8	75th: 15.0	Correlation (*r*): NA Copollutant models with: NA
Fung et al. (2006) Vancouver, Canada 1995–1999 ≥65 yr	Average across sites monitors $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	460–519	5.6	Max: 27.1	Correlation (*r*): −0.03 O_3, 0.36 NO_2, 0.23 CO, 0.42 SO_2, 0.34 $PM_{2.5}$ Copollutant models with: NA
Burnett et al. (1997) Toronto, Canada 1992–1994, summers only All ages	One monitor $PM_{10-2.5}$ directly measured by a dichotomous monitor.	464–466; 490; 480–486; 491–494, 496	10a	75th: 23 95th: 40 Max: 66	Correlation (*r*): 0.32 O_3, 0.45 NO_2, 0.42 CO, 0.49 SO_2, 0.72 $PM_{2.5}$ Copollutant models with: O_3, CO, NO_2, SO_2
†Powell et al. (2015) 119 U.S. counties 1999–2010 ≥65 yr	Average of across sites in each county $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	464–466, 480–487; 490–492	12.8a	75: 15.8	Correlation (*r*): NA Copollutant models with: NA

Table 5-34 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
†Samoli et al. (2016a) Five European cities 2001–2011 All ages	Average across sites in each city $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	466, 480–487; 490–492, 494, 496; 493	5.7–12.2	NR	Correlation (*r*): NA Copollutant models with: NA
†Lanzinger et al. (2016b)[b] Four European cities (UFIREG) 2011–2014 All ages	Average across sites in each city $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	J00–J99	4.7–9.8	Max: 21.6–44.6	Correlation (*r*): 0.40–0.61 $PM_{2.5}$, 0.58–0.78 PM_{10}, 0.37–0.43 NO_2 Copollutant models with: NA
†Stafoggia et al. (2013)[c] Six European cities (MED-PARTICLES) 2003–2013 ≥15 yr	Average across sites in each city $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	460–519	9.3–17.5	NR	Correlation (*r*): ≥0.5 $PM_{2.5}$ Madrid, Milan, Emilia-Romagna, 0 other cities, >0.60 with NO_2 Copollutant models with: $PM_{2.5}$, NO_2, O_3
†Atkinson et al. (2010) London, U.K. 2000–2005 0–14 yr, All ages	One monitor $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at collocated monitors.	J00–J99	7.0a	75th: 10.0 Max: 36.0	Correlation (*r*): 0.22 $PM_{2.5}$, 0.52 PM_{10} Copollutant models with: NR
†Alessandrini et al. (2013) Rome, Italy 2001–2004 All ages	One monitor $PM_{10-2.5}$ estimated by calculating difference between PM_{10} and $PM_{2.5}$ at a collocated monitor.	460–519	No Saharan dust days: 14.6 Saharan dust days: 20.7	NR	Correlation (*r*): 0.25 $PM_{2.5}$, 0.81 PM_{10} Copollutant models with: $PM_{2.5}$, O_3

Table 5-34 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
ED visits					
Peel et al. (2005) Atlanta, GA 1993–2000 All ages	One monitor Direct measurement of $PM_{10-2.5}$ concentration by a dichotomous monitor (Van Loy et al., 2000).	460–466, 477; 480–486; 491, 492, 496; 493, 786.09	19.2	90th: 32.3	Correlation (*r*): 0.55–0.68, CO, NO_2 Copollutant models with: NA
Tolbert et al. (2007) Atlanta, GA 1993–2004 All ages	One monitor Direct measurement of $PM_{10-2.5}$ concentration by a dichotomous monitor (Van Loy et al., 2000).	460–465, 460.0, 477; 480–486; 491, 492, 496; 493, 786.07, 786.09; 466.1, 466.11, 466.19	17.1	75th: 21.9 90th: 28.8 Max: 65.8	Correlation (*r*): 0.62 O_3, 0.47 NO_2, 0.47 CO, 0.17 SO_2, 0.47 $PM_{10-2.5}$ Copollutant models with: NA
†Malig et al. (2013) 35 California counties 2005–2008 All ages	Difference of collocated PM_{10} and $PM_{2.5}$ concentrations, assigned from the nearest monitoring station within 20 km of population-weighted zip code centroid.	460–519	5.6–34.4	NR	Correlation (*r*): 0.31 $PM_{2.5}$, 0.38 O_3, 0.14 CO Copollutant models with: $PM_{2.5}$, O_3, NO_2, CO, SO_2

Table 5-34 (Continued): Epidemiologic studies of $PM_{10-2.5}$ and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment/Measurement of $PM_{10-2.5}$ Concentrations	ICD Codes ICD-9 or ICD-10	Mean Concentration µg/m^3	Upper Percentile Concentrations µg/m^3	Copollutant Examination
Hospital admissions and ED visits, separately					
†Rodopoulou et al. (2014) Doña Ana County, NM 2007–2010 ≥18 yr	Three monitors $PM_{10-2.5}$ concentration estimated by calculating difference between PM_{10} and $PM_{2.5}$ concentrations; not clearly stated if $PM_{10-2.5}$ concentrations were averaged across monitors, if assignment came from the nearest monitor, or if PM_{10} and $PM_{2.5}$ monitors were collocated.	460–465, 466, 480–486, 490–493, 496	10.9	75th: 13 Max: 55.6	Correlation (*r*): −0.05 O_3 Copollutant models with: NA

CMAQ = Community Multi-Scale Air Quality model; MED-PARTICLES = particles size and composition in Mediterranean countries: geographical variability and short-term health effects; UFIREG = ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy.

[a]Median concentration

[b]Only four of the five cities had $PM_{10-2.5}$ data.

[c]Only six of the eight cities had $PM_{10-2.5}$ data.

†Studies published since the 2009 PM ISA.

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Recent multicity studies (Lanzinger et al., 2016b; Samoli et al., 2016a; Powell et al., 2015; Stafoggia et al., 2013) and single-city studies (Rodopoulou et al., 2014; Alessandrini et al., 2013; Atkinson et al., 2010) conducted in the U.S. and Europe that examined the association between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions provide evidence of positive associations that vary in terms of magnitude and precision (Figure 5-44), particularly in analyses of people of all ages. In a limited assessment of potential copollutant confounding, associations were often attenuated, but remained positive in copollutant models with $PM_{2.5}$, NO_2, and O_3 (Powell et al., 2015; Alessandrini et al., 2013; Stafoggia et al., 2013). The positive associations reported across these studies is supported by a meta-analysis focusing on $PM_{10-2.5}$ and respiratory hospital admissions that reported a RR = 1.01 (95% CI: 1.00, 1.02) (Adar et al., 2014). Additional analyses conducted by Adar et al. (2014) to assess potential copollutant confounding by $PM_{2.5}$ did not observe a consistent pattern in $PM_{10-2.5}$ associations as the correlation with $PM_{2.5}$ increased or when evaluating studies that examined associations with both $PM_{2.5}$ and $PM_{10-2.5}$.

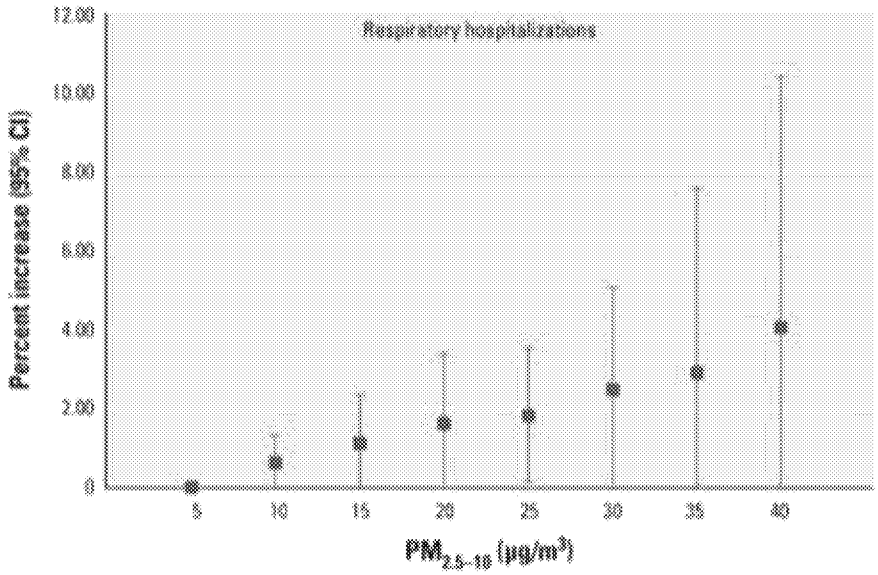
Additional single-city studies conducted in London, U.K. (Atkinson et al., 2010) and Rome, Italy, (Alessandrini et al., 2013) also contribute to the total body of evidence for respiratory-related hospital admissions. Atkinson et al. (2010) when examining a number of urban particles, examined associations with $PM_{10-2.5}$ and across single-day lags ranging from 0 to 6 days. The authors reported evidence of a positive association at lag 1 in an all ages analysis, but there was no evidence of an association for the other lags examined (quantitative results not presented). Instead of focusing on urban particles, Alessandrini et al. (2013) examined the role of Saharan dust on the relationship between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions. Across the entire study duration, the authors reported a 4.4% increase (95% CI: −0.53, 9.60) in hospital admissions at lag 0−5 days. However, when differentiating between Saharan and non-Saharan dust days, Alessandrini et al. (2013) observed that the overall association reported was primarily attributed to the Saharan dust days (13.5%) compared to the non-Saharan dust days (−0.30%).

Across the hospital admissions studies evaluated, a few of the studies conducted sensitivity analyses to examine the lag structure of associations and model specification. Both Stafoggia et al. (2013) and Lanzinger et al. (2016b) examined whether there is evidence of immediate (lag 0−1), delayed (lag 2−5), or prolonged (lag 0−5) effects of $PM_{10-2.5}$ on respiratory-related hospital admissions. In both studies, positive associations were observed across each of the lags, with the association largest in magnitude at lag 0−5, indicating a potential prolonged effect [(Stafoggia et al., 2013): lag 0−1, 1.0% [95% CI: 0.10, 1.8]; lag 2−5: 1.2% [95% CI: −1.1, 3.6]; lag 0−5: 2.0% [95% CI: −0.51, 4.5]; (Lanzinger et al., 2016b): lag 0−1, 7.4% [95% CI: 1.9, 12.7]; lag 2−5: 10.7% [95% CI: 4.7, 16.9]; lag 0−5: 13.9% [95% CI: 6.9, 21.3]]. However, in Stafoggia et al. (2013), as the lag days increased, the confidence intervals did as well, resulting in more uncertain estimates. The results of Stafoggia et al. (2013) and Lanzinger et al. (2016b) are supported by Samoli et al. (2016a) when examining single-day lags ranging from 0 to 10 days where positive associations were observed through lag Day 4, but the strongest

association in terms of magnitude and precision was a lag 1 (quantitative results not presented). Stafoggia et al. (2013) and Powell et al. (2015) both examined the influence of alternative approaches to account for temporal trends and the confounding effects of weather and found that results were relatively unchanged.

Similar to the 2009 PM ISA (U.S. EPA, 2009), compared to studies that examined short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions, fewer studies focused on ED visits with the evidence primarily limited to single-city studies. In analyses of all ages, there is no evidence of an association when examining the results from single-city studies. Rodopoulou et al. (2014) in a study conducted in Doña Ana County, NM reported a positive association for older adults, but no evidence of an association for an all ages analysis, which is consistent with the single-city studies evaluated in the 2009 PM ISA (Figure 5-44). However, Malig et al. (2013), in a study of 35 California counties, reported positive associations at lags 1 and 2 days, with the strongest association in terms of magnitude and precision at lag 1 (0.7% [95% CI: 0.3, 1.1]). The association with $PM_{10-2.5}$ was found to remain positive in copollutant models with O_3, NO_2, CO, SO_2, and $PM_{2.5}$. Additionally, associations were found to be slightly elevated in the warm compared to cold season, and robust to the exclusion of extreme $PM_{10-2.5}$ values (the highest and lowest 5% of calculated coarse particle levels) from the analysis. Rodopoulou et al. (2014) also examined the influence of season and extreme $PM_{10-2.5}$ concentrations and reported contradictory results to Malig et al. (2013), i.e., associations larger in magnitude in the cold season and that the $PM_{10-2.5}$ association increased in magnitude when excluding high $PM_{10-2.5}$ concentrations. Uncertainties in how $PM_{10-2.5}$ concentration was estimated in Rodopoulou et al. (2014) complicates the comparison between studies.

Recent studies of respiratory-related hospital admissions and ED visits provide an initial assessment of the C-R relationship, but is limited by the studies not conducting extensive empirical evaluations of alternatives to linearity, and whether there is evidence of a threshold below which effects are not observed. Malig et al. (2013) provides initial evidence of a linear relationship through an analysis where the inclusion of a squared term for $PM_{10-2.5}$ into the statistical model to account for possible nonlinearity did not improve the goodness of fit over the initial model that assumed linearity. Stafoggia et al. (2013) examined whether there was evidence of a threshold in a study of six European cities, which is similar the threshold analysis detailed for $PM_{2.5}$ (Section 5.1.10.6). As depicted in Table 5-45, the authors examined the percent increase in hospital admissions at various concentrations across the distribution of $PM_{10-2.5}$ concentrations, up to 40 $\mu g/m^3$, relative to 5 $\mu g/m^3$, and reported no evidence a threshold.



Source: Permission pending, Adapted from Stafoggia et al. (2013).

Figure 5-45 Concentration-response relationship between short-term $PM_{10-2.5}$ exposure and respiratory-related hospital admissions, lag 0–5, relative to 5 µg/m³.

5.3.6 Respiratory Effects in Healthy Populations

The 2009 PM ISA (U.S. EPA, 2009) evaluated a limited number of studies that examined the effects of short-term exposure to $PM_{10-2.5}$ on respiratory effects in healthy populations. No epidemiologic studies were available on $PM_{10-2.5}$ exposure and respiratory effects in healthy populations. Null findings were reported for lung function in populations of children, but their health status was not reported (Dales et al., 2008; Moshammer et al., 2006). Evidence for inflammation was inconsistent in controlled human exposure studies. Alexis et al. (2006) found evidence of pulmonary inflammation, as well as innate immune responses of airway macrophages, and increased levels of eotaxin in healthy individuals. Some of these responses were reduced by biological inactivation (i.e., heat-treatment of $PM_{10-2.5}$) implicating a role for endotoxin. Additionally, short-term exposure to $PM_{10-2.5}$ particles was also shown to elicit increases in polymorphonuclear leukocytes and inflammatory cytokines in healthy adults (Graff et al., 2009). However, Jr et al. (2004) reported no effect of short-term $PM_{10-2.5}$ exposure on markers of airway inflammation in healthy subjects. Animal toxicological studies employed noninhalation routes of exposure since inhalation exposure of rodents to $PM_{10-2.5}$ is technically difficult given that rodents are obligatory nasal breathers. A number of studies of involving noninhalation routes of exposure (i.e., oropharyngeal aspiration, intra-tracheal instillation) support a potential role of short-term $PM_{10-2.5}$ exposure in pulmonary oxidative stress and inflammation (Gilmour et al., 2007; Happo et al., 2007; Dick et al., 2003). Evidence for pulmonary injury, oxidative stress, inflammation, and morphological changes

was also provided by Gerlofs-Nijland et al. (2007); Gerlofs-Nijland et al. (2005) in studies involving intra-tracheal instillation of $PM_{10-2.5}$ and an animal model of cardiovascular disease.

5.3.6.1 Epidemiologic Studies

Recent studies have used scripted exposures of healthy adults alternating between rest and exercise in high- and low-pollution locations. These studies minimize uncertainty in the $PM_{10-2.5}$ exposure metric by measuring personal ambient $PM_{10-2.5}$ at the site of exposure (calculated as the difference between PM_{10} and $PM_{2.5}$). In Utrecht, the Netherlands, $PM_{10-2.5}$ exposure of 5 hours was associated with a decrease in FVC and an increase in eNO (Strak et al., 2012). However, the observed associations were small in magnitude and the authors did not report confidence intervals or other measures of precision. Two-hour $PM_{10-2.5}$ exposure was also associated with increased eNO, but not with any of the number of lung function metrics measured in a study of healthy adults in Barcelona, Spain (Kubesch et al., 2015). In a follow-up study using a similar design, Matt et al. (2016) reported FEV_1, FVC, and PEF decrements associated with $PM_{10-2.5}$. Results appeared to be transient, as associations were observed immediately after exposure, but not 7 hours later during a follow-up spirometry test (Matt et al., 2016). Inconsistent associations among the vast number of pollutants and outcomes analyzed within studies is a limitation of all the reviewed studies.

There is limited evidence in healthy children in Chile, Sweden, and Taiwan for associations with 24-hour average $PM_{10-2.5}$ concentrations (difference between PM_{10} and $PM_{2.5}$ measured at monitors). Repeated measures of respiratory symptoms and eNO were associated with $PM_{10-2.5}$ concentrations at a monitor within 1.5 or 3 km of home or school (Prieto-Parra et al., 2017; Carlsen et al., 2016). In a cross-sectional analysis, $PM_{10-2.5}$ averaged across city monitors were associated with decreases in FEV_1, FVC, MMEF, FEV_1/FVC, and MMEF/FVC (Chen et al., 2015a). Cross-sectional measurements are generally less informative than repeated measures study designs because they do not establish a temporal relationship between the exposure and outcome of interest. Other findings in children are inconsistent, but do not provide insight into the respiratory effects of $PM_{10-2.5}$ exposure in healthy people because they are for a population with 66% prevalence of asthma or allergy (Chen et al., 2012; Chen et al., 2011a) or infants on cardiorespiratory monitors who may not spend much time outdoors away from home (Peel et al., 2011).

5.3.6.2 Controlled Human Exposure

In a recent study, Behbod et al. (2013) exposed subjects to $PM_{10-2.5}$ CAPs and measured multiple markers of airway inflammation, but relative to filtered air, no significant airway (sputum) responses were found (Table 5-35).

Table 5-35 Study-specific details from a controlled human exposure study of short-term $PM_{10-2.5}$ exposure and respiratory effects in a healthy population.

Study	Study Design	Disease Status; n; Sex; (Age)	Exposure Details (Concentration; Duration; Comparison Group)	Endpoints Measured
Behbod et al. (2013)	Double-blind, randomized cross-over block design	Healthy nonsmokers; n = 35; 11 M, 12 F (18–60 yr)	234.7 μg/m^3 $PM_{2.5}$ (IQR: 52.4 μg/m^3) for 130 min (120-min exposure + 10 min to complete tests) at rest. Comparison groups were either (1) filtered air or (2) medical air; a minimum 2-week washout period was used between exposures.	Sputum (pre- and 24-hour post-exposure): Total cell and neutrophil counts

BAL = bronchoalveolar lavage; IL-6 = interleukin-6, IL-8 = interleukin-8, IQR = interquartile range.

5.3.6.3 Animal Toxicological Studies

Recent studies involving intra-tracheal instillation confirm previous results showing that $PM_{10-2.5}$ collected during different seasons and from different locations exhibits variable potency in terms of pulmonary injury, inflammation, and morphologic changes (Lippmann et al., 2013a; Mirowsky et al., 2013; Halatek et al., 2011). In addition, two recent animal inhalation studies provide evidence for respiratory effects in healthy populations resulting from short-term exposure to $PM_{10-2.5}$. Amatullah et al. (2012) found that a 4-hour inhalation exposure of BALB/c mice to $PM_{10-2.5}$ CAPs in Toronto increased baseline total respiratory resistance ($p < 0.05$) and maximum response to methacholine ($p < 0.01$) immediately after exposure. In addition, quasi-static compliance was decreased ($p < 0.01$) and quasi-static elastance was increased ($p < 0.01$). These changes indicate airway obstruction. Amatullah et al. (2012) also found increased total cells and macrophages in the bronchoalveolar lavage fluid (BALF) ($p < 0.05$). Aztatzi-Aguilar et al. (2015) showed that multiday inhalation exposure of Sprague Dawley rats to $PM_{10-2.5}$ CAPs in Mexico City resulted in increased IL-6 protein in lung tissue ($p < 0.05$). In addition, a reduction in angiotensin converting enzyme was observed ($p < 0.05$). Angiotensin converting enzyme is a component of the RAS and regulates levels of the potent vasoconstrictor angiotensin II. Since deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents, recent animal toxicological studies links deposition in the nose to changes in pulmonary function including increased airway responsiveness, inflammation in the lower airways, and changes in the RAS. Additional study details for these recent toxicological studies are found in Table 5-36.

Table 5-36 Study-specific details from animal toxicological studies of short-term $PM_{10-2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Amatullah et al. (2012) Species: Mouse Sex: Female Strain: BALB/c Age/Weight: 6–8 weeks, 18 g	$PM_{10-2.5}$ CAPs Toronto Particle size: $PM_{10-2.5}$ Control: HEPA-filtered air	Route: Nose-only inhalation Dose/Concentration: $PM_{10-2.5}$ 793 µg/m³, duration: 4 h Time to analysis: At end of exposure Modifier: Baseline ECG	Pulmonary function—airways resistance, quasi-static elastance BALF cells
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	$PM_{10-2.5}$ CAPs Mexico City Particle size: $PM_{10-2.5}$ Control: Filtered air	Route: Inhalation Dose/Concentration: $PM_{10-2.5}$ 32 µg/m³ Duration: Acute 5 h/day, 3 days Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of RAS and kalikrein-kinin endocrine system • Heme oxygenase-1

BALF = bronchoalveolar lavage fluid; ECG = electrocardiogram; IL-6 = interleukin 6; RAS = renin-angiotensin system.

5.3.6.4 Summary of Respiratory Effects in Healthy Populations

Epidemiologic and controlled human exposure studies examining healthy populations do not consistently support a relationship between $PM_{10-2.5}$ and lung function or pulmonary inflammation. Animal toxicological studies provide evidence for decrements in lung function, inflammation, oxidative stress, and upregulation of the RAS system following short-term inhalation exposure to $PM_{10-2.5}$. Support for some of these findings in animals are provided by studies using noninhalation routes of exposure.

5.3.7 Respiratory Mortality

Studies that examine the association between short-term $PM_{10-2.5}$ exposure and cause-specific mortality outcomes, such as respiratory mortality, provide additional evidence for $PM_{10-2.5}$-related respiratory effects, specifically whether there is evidence of an overall continuum of effects. In the 2009 PM ISA (U.S. EPA, 2009), only a few studies examined the association between short-term $PM_{10-2.5}$ exposure and respiratory mortality, with only one U.S. based multicity study (Zanobetti and Schwartz, 2009). Across studies, there was evidence of generally positive associations with respiratory mortality even though studies used a variety of approaches to estimate $PM_{10-2.5}$ concentrations, but confidence intervals were wide in the single-city studies evaluated. Overall, there was limited evaluation of the

potential confounding effects of gaseous pollutants and the influence of model specification on the associations observed.

Recent multicity epidemiologic studies that examined associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality provide evidence of positive associations in some locations, but not in others (Figure 11-27). However, a meta-analysis (Adar et al., 2014) indicates a $PM_{10-2.5}$ association similar in magnitude as the multicity U.S. based study (Zanobetti and Schwartz, 2009) evaluated in the 2009 PM ISA (U.S. EPA, 2009). Unlike the studies evaluated in the 2009 PM ISA, some recent studies have also further evaluated the $PM_{2.5}$-respiratory mortality relationship by examining cause-specific respiratory mortality outcomes (i.e., COPD, pneumonia, and LRTI) (Samoli et al., 2014; Janssen et al., 2013). Overall, the results reported in the studies that examine cause-specific respiratory mortality outcomes are generally consistent with the results for all respiratory mortality, but the smaller number of mortality events observed results in estimates with larger uncertainty. As a result, this section focuses on studies that examine all respiratory mortality outcomes and address uncertainties and limitations in the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality, specifically: potential copollutant confounding, lag structure of associations, and effect modification by season and temperature.

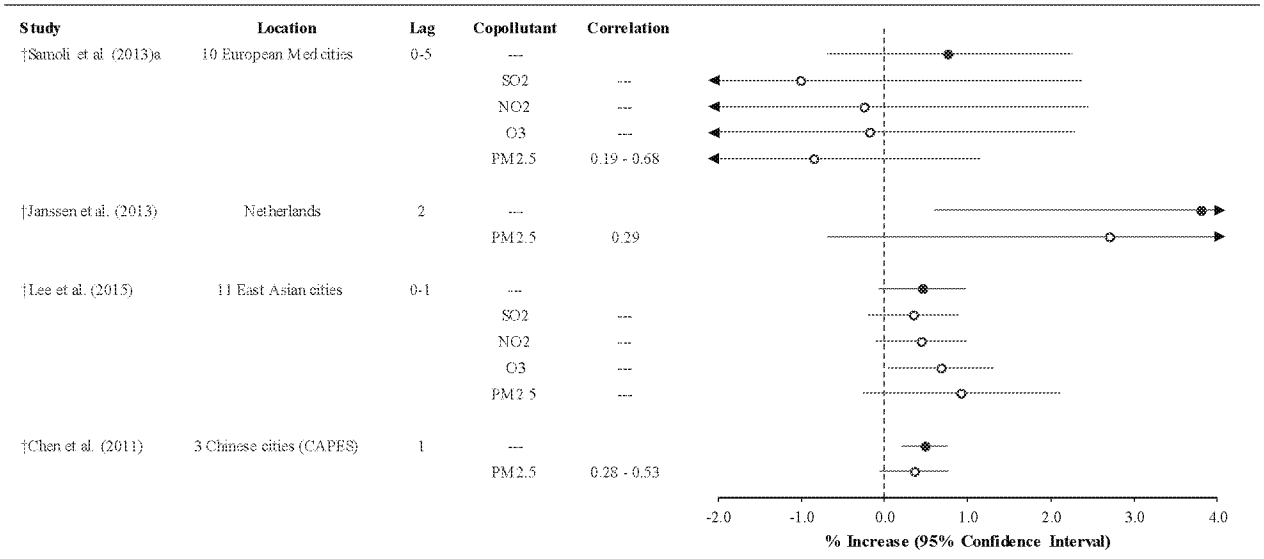
5.3.7.1 Characterizing the $PM_{10-2.5}$-Respiratory Mortality Relationship

Recent epidemiologic studies conducted additional analyses that address some of the uncertainties and limitations of the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality identified in the 2009 PM ISA (U.S. EPA, 2009). Specifically, recent studies provide additional information on copollutant confounding, lag structure of associations, and seasonal associations. However, similar to those studies evaluated in the 2009 PM ISA, the approaches used to estimate $PM_{10-2.5}$ concentrations varies across studies and it remains unclear if the level of exposure measurement error varies by each approach (Table 11-9). Overall, these studies provide initial evidence that: $PM_{10-2.5}$-respiratory mortality associations remain positive but may be attenuated in copollutant models; $PM_{10-2.5}$ effects on respiratory mortality tend to occur within the first few days of exposure (i.e., lags 0 to 2 days); and it remains unclear if there are seasonal differences in associations.

5.3.7.1.1 Copollutant Confounding

Consistent with the evaluation of total (nonaccidental) mortality, the studies evaluated in the 2009 PM ISA (U.S. EPA, 2009) provided limited information on the potential confounding effects of gaseous pollutants and $PM_{2.5}$ on the relationship between short-term $PM_{10-2.5}$ exposure and respiratory mortality. Recent multicity studies (Lee et al., 2015; Janssen et al., 2013; Samoli et al., 2013; Chen et al., 2011b) and a meta-analysis (Adar et al., 2014) provide additional information concerning the role of copollutants on the $PM_{10-2.5}$-respiratory mortality relationship.

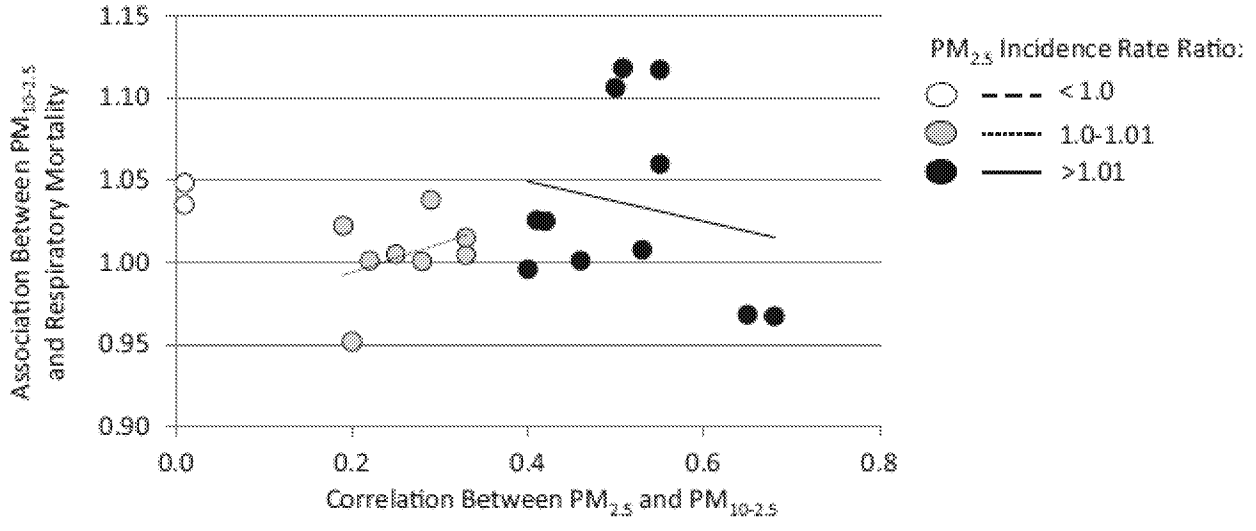
When focusing on potential copollutant confounding of the $PM_{10-2.5}$-respiratory mortality relationship by $PM_{2.5}$, there is evidence that the association generally remains positive (Figure 5-46). However, Samoli et al. (2013) in a study of 10 European Mediterranean cities within the MED-PARTICLES project did not find any evidence of $PM_{10-2.5}$-respiratory mortality association in copollutant models with $PM_{2.5}$. Unlike the other studies evaluated, the authors only presented copollutant model results for lag 0–5 days, which is a lag structure that is longer and inconsistent with the larger body of evidence (Section 5.3.7.1.2).



Note: †Studies published since the 2009 PM ISA. a = copollutant results only presented for a lag of 0–5 days. Corresponding quantitative results are reported in Supplemental Material (U.S. EPA, 2018).

Figure 5-46 Percent increase in respiratory mortality for a 10 µg/m^3 increase in 24-hour average $PM_{10-2.5}$ concentrations in single- and copollutant models.

The studies that provide evidence of a $PM_{10-2.5}$-respiratory mortality association that remains positive in copollutant models with $PM_{2.5}$ are supported by analyses conducted by Adar et al. (2014) in the context of a meta-analysis. When examining studies that conducted copollutant models with $PM_{2.5}$, Adar et al. (2014) observed that the $PM_{10-2.5}$-respiratory mortality association was similar in magnitude to that observed in single-pollutant models (quantitative results not provided). The results from copollutant models were further supported when stratifying $PM_{10-2.5}$-mortality estimates by the correlation with $PM_{2.5}$ (low, $r < 0.35$; medium, $r = 0.35$ to <0.5; high, $r > 0.5$). The authors observed evidence of positive associations for the medium and high correlation categories that were similar in magnitude, but had wide confidence intervals. However, there was no evidence of an association for the low correlations. Adar et al. (2014) further examined potential copollutant confounding by $PM_{2.5}$ through an analysis focusing on whether $PM_{10-2.5}$-mortality associations were present when the correlation between $PM_{2.5}$ and $PM_{10-2.5}$ increased and when $PM_{2.5}$ was also associated with mortality. As highlighted in Figure 5-47, there was evidence of positive $PM_{10-2.5}$-respiratory mortality associations at both low and high correlations as well as low and high magnitudes of the $PM_{2.5}$-respiratory mortality association (Figure 5-47).



Source: Permission pending, Adar et al. (2014).

Figure 5-47 Associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality as a function of the correlation between $PM_{10-2.5}$ and $PM_{2.5}$ stratified by strength of the association with $PM_{2.5}$.

Across the studies that examined potential copollutant confounding, only a few examined gaseous pollutants (Lee et al., 2015; Samoli et al., 2013) and the results contradict one another (see Figure 5-46).

As a result, it remains unclear whether gaseous copollutants confound the $PM_{10-2.5}$-respiratory mortality association.

Collectively, the recent epidemiologic studies that examined potential copollutant confounding provide initial evidence that $PM_{10-2.5}$-respiratory mortality associations remain generally positive in copollutant models particularly with $PM_{2.5}$. However, the lack of information on the correlations among the pollutants examined and the limited analyses of gaseous pollutants complicates the interpretation of the copollutant model results.

5.3.7.1.2 Lag Structure of Associations

Multicity epidemiologic studies that examined cause-specific mortality in the 2009 PM ISA (U.S. EPA, 2009) observed immediate effects on respiratory mortality attributed to short-term $PM_{10-2.5}$ exposure, with consistent positive associations observed at lags ranging from 0 to 2 days. However, the majority of these studies either examined single-day lags or selected lags a priori. Recent multicity studies have conducted more extensive examinations of the lag structure of associations by examining multiple sequential single-day lags or examining whether there is evidence of immediate (i.e., lag 0–1 days), delayed (i.e., lag 2–5 days), or prolonged (i.e., lag 0–5 days) effects of short-term $PM_{10-2.5}$ exposure on respiratory mortality.

Across the studies that examined single-lag days, most of the studies focused on lags within the range of 0 to 2 days. Although a few studies extended out to a longer duration, collectively the studies provided evidence that was generally in agreement with one another. Janssen et al. (2013), in a study conducted in the Netherlands, examined single-day lags of 0 to 3 days and reported no evidence of an association at lag 0 and 1 day. The largest association in terms of magnitude and precision was for lag 2 days (3.8% [95% CI: 0.6, 7.2]). Chen et al. (2011b), within the CAPES study, reported evidence of an immediate effect between short-term $PM_{10-2.5}$ exposure and respiratory mortality by observing evidence of a positive association at lag 1 and no evidence of an association at lag 0 and 2 days. Stafoggia et al. (2017), in a study of eight European cities, examined single-day lags ranging from 0 to 10 days also reported evidence of an immediate effect with positive associations at lags 0 and 1 day. However, the authors found evidence of positive associations at longer lags (i.e., lag 4 and 5), but confidence intervals were wide. The results across the studies that examined a series of single-day lags is further supported by the meta-analysis by Adar et al. (2014) where an examination of single-day lag risk estimates across studies found positive associations across lags ranging from 0 to 2 days with the strongest association in terms of magnitude and precision occurring at lag 1.

Although the studies that examined a series of single-day lags tend to support a $PM_{10-2.5}$-respiratory mortality association within the first few days after exposure, Samoli et al. (2013), in the MED-PARTICLES project, did not provide further support for this lag structure of associations. The authors examined both a series of multiday lags as well as single-day lags through a polynomial

distributed lag over 0–7 days. In the multiday lag analysis, Samoli et al. (2013) reported the strongest evidence of an association for a delayed effect (i.e., lag 2–5 days) (0.72% [95% CI: −0.31, 1.8]), with no evidence of an association at lag 0–1 days. This observation was confirmed when examining the polynomial distributed lag provided evidence of positive associations only at lags 3,4, and 5 (quantitative results not presented).

Overall, studies that examined the lag structure of associations generally support that short-term $PM_{10-2.5}$ exposure contributes to respiratory mortality effects within the first few days after exposure, ranging from 0–2 days. However, there is initial evidence that the $PM_{10-2.5}$-respiratory mortality association may be more delayed.

5.3.7.1.3 Effect Modification

Season

An examination of potential seasonal differences in associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality in the 2009 PM ISA (U.S. EPA, 2009) was limited to one U.S. multicity study (Zanobetti and Schwartz, 2009) that provided initial evidence of associations being larger in magnitude in the spring and summer. Although still limited in number, some recent multicity studies conducted an examination of potential seasonal differences in associations (Lee et al., 2015; Samoli et al., 2013).

Samoli et al. (2013), in the MED-PARTICLES project, only examined warm (April–September) and cold months (October–March). In analyses focusing on lag 0–5 days, the authors observed evidence of positive associations in both seasons, with associations larger in magnitude during the warm season (1.21% [95% CI: −2.0, 4.6]) compared to the cold season (0.30% [95% CI: −1.8, 2.5]), but confidence intervals were wide. Lee et al. (2015), in a study conducted in 11 east Asian cities, observed a different pattern of seasonal associations. The authors reported larger associations in the cold season (1.2% [95% CI: 0.16, 2.3]) compared to the warm (0.42% [95% CI: −0.30, 1.2]). It is unclear why these results differ from the other studies, but mean $PM_{10-2.5}$ concentrations and mean temperature tended to be higher across the cities in Lee et al. (2015) compared to the cities in the other studies evaluated in this section. Overall, the inconsistent evidence across studies does not provide additional information on the seasonal pattern of associations between short-term $PM_{10-2.5}$ exposure and respiratory mortality.

Temperature

In addition to examining whether there is evidence that warm temperatures modify the $PM_{10-2.5}$-respiratory mortality relationship by conducting seasonal analyses, a recent study also examined whether there is evidence that high temperature days modify the $PM_{10-2.5}$-respiratory mortality

relationship. Although in all-year analyses, Pascal et al. (2014) reported no evidence of an association between short-term $PM_{10-2.5}$ exposure and respiratory mortality, the authors examined whether temperature modified the relationship. Pascal et al. (2014) examined the impact of temperature on the $PM_{10-2.5}$-respiratory mortality relationship across nine French cities by comparing associations on warm and nonwarm days, where warm days were defined as those days where the mean temperature exceeded the 97.5th percentile of the mean temperature distribution. When calculating the interaction ratio, which estimated the extra PM effect due to warm days, the authors observed no evidence of a positive modifying effect of warm days on respiratory mortality.

5.3.8 Summary and Causality Determination

Based on a small number of epidemiologic studies observing associations with some respiratory effects and limited evidence from experimental studies to support biological plausibility, the 2009 PM ISA (U.S. EPA, 2009) concluded that the relationship between short-term exposure to $PM_{10-2.5}$ and respiratory effects is suggestive of a causal relationship. Epidemiologic findings were consistent for respiratory infection and combined respiratory-related diseases, but not for COPD. Studies were characterized by overall uncertainty in the exposure assignment approach and limited information regarding potential copollutant confounding. Controlled human exposure studies of short-term $PM_{10-2.5}$ exposure found no lung function decrements and inconsistent evidence for pulmonary inflammation in healthy individuals or human subjects with asthma. Animal toxicological studies were limited to those using noninhalation (e.g., intra-tracheal instillation) routes of $PM_{10-2.5}$ exposure. Recent studies strengthen the evidence base for asthma exacerbation and respiratory mortality, but they do not rule out chance and confounding. The evidence for the relationship between short-term exposure to $PM_{2.5}$ and effects on the respiratory system is summarized in Table 5-37, using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

Table 5-37 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Asthma exacerbation			
Consistent epidemiologic evidence from a limited number of multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in asthma-related hospital admissions and ED visits. Evidence mostly from single-city studies conducted in the U.S.	Section 5.3.2.1	9.7–16.2 μg/m^3

Table 5-37 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Uncertainty regarding confounding by copollutants	Potential copollutant confounding for asthma-related hospital admissions and ED visits is examined in a few studies, with some evidence that associations remain robust in models with gaseous pollutants and $PM_{2.5}$.	Section 5.3.2.1	
Uncertainty regarding exposure measurement error	Uncertainty in using $PM_{10-2.5}$ concentrations, estimated by differencing PM_{10} and $PM_{2.5}$ concentrations, as exposure surrogates, is not addressed.		
Limited coherence in epidemiologic studies across the continuum of effects	Providing support for asthma exacerbation are findings of associations for respiratory symptoms in children. There is no evidence for association with lung function decrements, and inconsistent evidence for eNO.	Section 5.3.2.2 Section 5.3.2.3 Section 5.3.2.4	
Inconsistent evidence from controlled human exposure studies	In adults with asthma, measures of lung function are unaffected. Results for pulmonary inflammation were inconsistent, with one study finding many effects on immune function.	Section 5.3.2.4.2 Alexis et al. (2014)	90 $\mu g/m^3$
Biological plausibility	Evidence from one controlled human exposure study provides biological plausibility with epidemiologic findings for allergic asthma, the most common asthma phenotype in children.		
Respiratory mortality			
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{10-2.5}$ concentrations	Associations are observed in single and multicity studies, with effects tending to occur between 0–2 days.	Section 5.3.7	
Uncertainty regarding confounding by copollutants and exposure measurement error	Potential copollutant confounding is examined in a few studies, with some evidence that associations remain robust in models with $PM_{2.5}$.	Section 5.3.7	
Uncertainty regarding exposure measurement error	Uncertainty in using $PM_{10-2.5}$ concentrations, estimated by differencing PM_{10} and $PM_{2.5}$ concentrations, as exposure surrogates, is not addressed.	Section 3.3.1	

Table 5-37 (Continued): Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
Some coherence with underlying causes of mortality	COPD and respiratory infection evidence provide some coherence.	Section 5.3.3 Section 5.3.4	
Exacerbation of COPD, respiratory infection and combined respiratory-related diseases			
Limited epidemiologic evidence and uncertainty regarding $PM_{10-2.5}$ independent effects	Generally positive associations for COPD-related hospital admissions in a limited number of studies conducted in the U.S., Canada, and Asia. Evidence is inconsistent for COPD ED visits.	Section 5.3.3.1	5.6–24.8 μg/m^3
	Generally positive associations ED visits for acute respiratory infection, pneumonia, and combinations of respiratory infections in a limited number of studies in the U.S., Canada, and Asia.	Section 5.3.4.1	5.6–24.8 μg/m^3
	Generally positive associations are observed for combined respiratory-related disease hospital admissions in single-city and multicity studies conducted in the U.S., Canada, and Europe. Evidence is inconsistent for combined respiratory-related disease visits.	Section 5.3.5	
Respiratory effects in healthy populations			
Inconsistent evidence from epidemiologic studies	A limited number of panel studies in healthy adults reported inconsistent evidence of associations with lung function and pulmonary inflammation.	Section 5.3.6.1	
Inconsistent evidence from controlled human exposure studies	Evidence is inconsistent for pulmonary inflammation.	Section 5.3.6.2 Behbod et al. (2013)	235 μg/m^3
Some evidence from toxicological studies at relevant concentrations	Results show altered lung function and pulmonary inflammation in rodents exposed by inhalation to $PM_{10-2.5}$ CAPs.	Amatullah et al. (2012) Aztatzi-Aguilar et al. (2015)	32–793 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

1

Recent epidemiologic findings more consistently link $PM_{10-2.5}$ to asthma exacerbation than studies reported in the 2009 PM ISA (U.S. EPA, 2009). These studies of hospital admission and ED visits include children older than 5 years. These findings are supported by epidemiologic studies observing respiratory symptoms in children and by a controlled human exposure study showing PM-related effects on inflammation and the immune system. There is limited evidence that associations remain robust in models with gaseous pollutants and $PM_{2.5}$. Recent, but limited, epidemiologic findings are also more consistent for COPD exacerbation and combined respiratory-related diseases compared with studies reported in the 2009 PM ISA. However, the evidence for COPD hospital admissions is inconsistent across several U.S. cities and for direct $PM_{10-2.5}$ measurements. Recent epidemiologic findings for respiratory infection differ than findings reported in the 2009 ISA in that they indicate associations with pneumonia, but not combinations of respiratory infections. The respiratory effects related to short-term $PM_{10-2.5}$ exposure in healthy individuals remain inconsistent, although some controlled human exposure and animal toxicological studies show effects. The evidence base for respiratory mortality is expanded since the 2009 PM ISA (U.S. EPA, 2009) and is generally supportive of associations with short-term exposure to $PM_{10-2.5}$. Studies provide initial evidence that $PM_{10-2.5}$-respiratory mortality associations remain positive but may be attenuated in copollutant models. In addition, $PM_{10-2.5}$ effects on respiratory mortality tend to occur within the first few days of exposure (i.e., lags 0 to 2 days). Across most of these respiratory outcome groups, copollutant confounding remains uncertain. An uncertainty spanning all epidemiologic studies examining associations with $PM_{10-2.5}$ is the lack of a systematic evaluation of the various methods used to estimate $PM_{10-2.5}$ concentrations and the resulting uncertainty in the spatial and temporal variability in $PM_{10-2.5}$ concentrations compared to $PM_{2.5}$ (Section 2.5.1.2.3 and Section 3.3.1.1). **Overall, the collective evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term $PM_{10-2.5}$ exposure and respiratory effects.**

5.4 Long-Term $PM_{10-2.5}$ Exposure and Respiratory Effects

The 2009 PM ISA concluded that the evidence was inadequate to assess the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects (U.S. EPA, 2009).[60] At that time, the evidence consisted of a single epidemiologic study. Some recent epidemiologic findings link $PM_{10-2.5}$ to lung function metrics (Section 5.4.2), the development of asthma (Section 5.4.3), and respiratory infection (Section 5.4.5) in children. However, there is little or no evidence for the development of allergic disease (Section 5.4.4), severity of asthma (Section 5.4.6), or respiratory effects in healthy populations (Section 5.4.7). In all recent studies, $PM_{10-2.5}$ concentrations were estimated by LUR models, dispersion models, or by subtracting monitored $PM_{2.5}$ concentrations from monitored PM_{10} concentrations. The major uncertainties for these studies involve the potential for exposure measurement error, especially

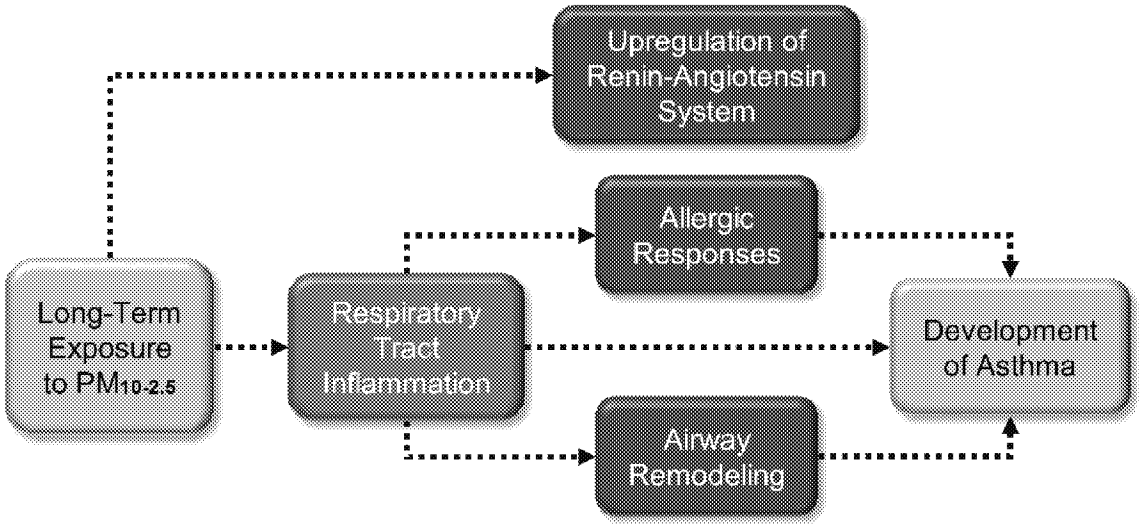
[60] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.

relating to the errors due to subtracting $PM_{2.5}$ concentration from PM_{10} concentration, notably when the monitors are not collocated, and the potential for confounding related to copollutants. Experimental evidence is limited to a single inhalation exposure in healthy animals, although additional studies using noninhalation routes of exposure provide biological plausibility for a relationship between long-term exposure to $PM_{10-2.5}$ and asthma severity.

5.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory health effects resulting from long-term exposure to $PM_{10-2.5}$. Figure 5-48 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" long-term exposure to $PM_{10-2.5}$ may lead to respiratory health effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.4.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). Insoluble and soluble components of $PM_{10-2.5}$ may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate reactive oxygen species (ROS) and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-48 Potential biological pathways for respiratory effects following long-term $PM_{10-2.5}$ exposure.

Evidence that long-term exposure to $PM_{10-2.5}$ may affect the respiratory tract generally informs one proposed pathway (Figure 5-48). It begins with respiratory tract inflammation and leads to allergic responses and airway remodeling that may underly the development or worsening of asthma. Epidemiologic evidence links long-term exposure to $PM_{10-2.5}$ and eNO, a marker of airway inflammation (Dales et al., 2008). Supportive evidence is provided by several animal toxicological studies involving intra-tracheal instillation (Liu et al., 2014; He et al., 2013a; He et al., 2013b). In these studies, multiple exposures to dust storm-associated $PM_{10-2.5}$ resulted in allergic inflammation and airway remodeling in nonallergic mice and enhanced allergen-induced responses in allergic mice. These findings are supportive of a link between long-term $PM_{10-2.5}$ exposure and incident asthma (Section 5.4.3). This proposed pathway provides biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.4.9).

In addition, a study of long-term $PM_{10-2.5}$ exposure in animals (Aztatzi-Aguilar et al., 2015) found decreases in tissue levels of heme oxygenase-1 and IL-6, markers of oxidative stress and inflammation, respectively. Increases in mRNA and protein levels of angiotensin receptor Type 1 and mRNA levels of angiotensin converting enzyme, which are components of the RAS, were also observed. Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. Deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways

(i.e., the nose) of rodents and to result in a much smaller fraction deposited in the lower respiratory tract compared with humans. This study links deposition of $PM_{10-2.5}$ in the nose to increased activity of the RAS and to a possible dampening of oxidative stress and inflammation in the lung.

5.4.2 Lung Function and Lung Development

As evaluated in the 2009 PM ISA (U.S. EPA, 2009), a cross-sectional analysis of 1,613 schoolchildren in Windsor, Ontario reported that a 5 ug/m^3 increase in $PM_{10-2.5}$ was not associated with percent predicted FEV_1 (0.26 [95% CI: −4.22, 4.74]) and was associated with small, imprecise (i.e., wide 95% CIs) increase in percent predicted FVC: (1.10 [95% CI: −8.11, 10.39]) (Dales et al., 2008). Recent analyses of European birth cohorts have observed consistent associations between $PM_{10-2.5}$ and an array of lung function metrics. In the PIAMA cohort, $PM_{10-2.5}$ estimated at children's current addresses was associated with decreases in FEV_1, FVC, and FEF_{25-75} measures collected at age 8 and 12 (Gehring et al., 2015a). Similarly, in an ESCAPE project analysis of five European cohorts, $PM_{10-2.5}$ estimates at both birth address and current address were negatively associated with FEV_1 measured at ages 6 and 8, but the effect was stronger when current address was used in the exposure assignment (Gehring et al., 2013). $PM_{10-2.5}$ at current address was also associated with higher odds of FEV_1 <85% of predicted values (OR: 1.81 [95% CI: 0.94, 3.47]), a clinically significant indicator of impaired lung function.

Cross-sectional studies of schoolchildren in 24 Taiwanese provinces (Chen et al., 2015a) and 9−10-year olds participating in the Child Heart and Health Study in England (Barone-Adesi et al., 2015) provided inconsistent evidence of an association between $PM_{10-2.5}$ and lung function. While Chen et al. (2015a) reported reductions of 102 ml (95% CI: 16, 189 ml) in FEV_1 and 121 ml (95% CI: 15, 227 ml) in FVC per 5 μg/m^3 increase in $PM_{10-2.5}$ over the past 2 months, Barone-Adesi et al. (2015) did not observe any associations between annual $PM_{10-2.5}$ exposure and the same lung function metrics. Additionally, it is unclear whether Chen et al. (2015a) estimated $PM_{10-2.5}$ using collocated PM_{10} and $PM_{2.5}$ monitors.

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term exposure to $PM_{10-2.5}$ on pulmonary function in adults. Results for the various indices of pulmonary function were inconsistent among adults participating in the ESCAPE project (Adam et al., 2015). $PM_{10-2.5}$ was associated with decrements in FEV_1 and FVC in a cross-sectional analysis, but an increase in FEV_1 in longitudinal analyses. Due to the strengths of a longitudinal study design compared to a cross-sectional design, it's possible that the negative association may have been the result of unmeasured confounding in the cross-sectional analysis.

5.4.3 Development of Asthma

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and the development of asthma available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). A few recent studies report associations between $PM_{10-2.5}$ and asthma incidence. In the PIAMA cohort in the Netherlands (Gehring et al., 2015a) and a pooled analysis of four European birth cohorts (Gehring et al., 2015b), asthma incidence was associated with $PM_{10-2.5}$ concentrations outside birth residences. The associations were attenuated, but still positive when $PM_{10-2.5}$ concentrations were assigned at the address of the participant at the time of follow-up. This indicates the potential importance of early life exposures.

Studies examining asthma prevalence in children reported contrasting evidence. The Gehring et al. (2015b) pooled analysis, discussed above, observed inconsistent evidence of an association across cohorts, and reported a null association in a meta-analysis combining results from all cohorts. Another ESCAPE project analysis of five European birth cohorts estimated $PM_{10-2.5}$ at participants' birth addresses and addresses at age 4 and age 8 (Mölter et al., 2014). Birth and current address $PM_{10-2.5}$ was not associated with higher odds of prevalent asthma at age 4. However, $PM_{10-2.5}$ estimated at both birth and current address was associated with an increase in odds of asthma by age 8. Contrary to the results for asthma incidence, the association was higher in magnitude and more precise when asthma prevalence was related to current address $PM_{10-2.5}$ concentrations (OR: 1.16 [95% CI: 0.93, 1.44]) rather than birth address exposure (1.10 [0.72, 1.69]).

No recent studies have examined subclinical effects underlying the development of asthma in association with long-term exposure to $PM_{10-2.5}$. A cross-sectional analysis of 1,613 schoolchildren in Windsor, Ontario, reviewed in the 2009 PM ISA (U.S. EPA, 2009), reported a null association between $PM_{10-2.5}$ and Ln(eNO) (Dales et al., 2008). Results from a prior CHS analysis (Bastain et al., 2011) showed that elevated eNO was associated with increased risk of new onset asthma.

In addition to studies conducted among children, one epidemiologic study evaluated the effects of long-term $PM_{10-2.5}$ exposure in adults. An ESCAPE project analysis also examined associations between $PM_{10-2.5}$ and incident asthma (Jacquemin et al., 2015). In a meta-analysis of all cohorts, annual $PM_{10-2.5}$ was not associated with higher odds of incident asthma (OR: 0.99 [95% CI: 0.87, 1.14]).

Animal toxicological studies related to the development of asthma are typically conducted in nonallergic animal models. Inhalation exposure of rodents to $PM_{10-2.5}$ is technically difficult since rodents are obligatory nasal breathers. A group of recent studies examined the effects of long-term $PM_{10-2.5}$ using Asian sand dust and noninhalation routes of exposure (i.e., intra-tracheal instillation). Results provide biological plausibility for a potential role of $PM_{10-2.5}$ in allergic inflammation and airway remodeling (Liu et al., 2014; He et al., 2013a; He et al., 2013b).

5.4.4 Development of Allergic Disease

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and the development of allergic disease available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). A small number of recent epidemiologic studies examined the association between long-term exposure to $PM_{10-2.5}$ and allergic disease. The relation between early-life exposure to $PM_{10-2.5}$ and allergic sensitization at age 4 and 8 years was examined in the ESCAPE pooled analysis of five European cohorts (Gruzieva et al., 2014). There were no clear associations between $PM_{10-2.5}$ concentrations estimated at birth address and sensitization at age 4 or age 8. Similarly, another European birth cohort pooled analysis did not observe an association between $PM_{10-2.5}$ and rhinoconjunctvitis (Gehring et al., 2015b). The PIAMA cohort reported on associations between $PM_{10-2.5}$ and allergic outcomes (Gehring et al., 2015a) noting that $PM_{10-2.5}$ was associated with increases in self-reported hay fever, rhinitis and allergic sensitization during the first 11 years of life (ORs ranging from 1.3 to 1.6 per 5 $\mu g/m^3$ increase). In a 2006 U.S. National Health Interview Survey (NHIS) cross-sectional analysis, $PM_{10-2.5}$ was examined as a potential predictor of allergy in children aged 3−17 years living within 20 miles of an air-quality monitor (Parker et al., 2009). $PM_{10-2.5}$ was not associated with respiratory allergy/hay fever.

5.4.5 Respiratory Infection

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and respiratory infection available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recently, an ESCAPE project study examined respiratory infections in relation to $PM_{10-2.5}$ (MacIntyre et al., 2014b). $PM_{10-2.5}$ estimated at birth residence was associated with an imprecise increase in odds of pneumonia in the first 36 months of life (OR: 1.24 [95% CI: 1.03, 1.5] per 5 ug/m^3 increase), but was not associated with increased odds of otitis media or croup. A sensitivity analysis looking at alternative outcome windows showed the strongest association between long-term $PM_{10-2.5}$ and pneumonia diagnosed in the first year of life (OR: 1.46 [95% CI: 1.11, 1.92]). The association between $PM_{10-2.5}$ and pneumonia at 36 months was attenuated, but still positive in a two-pollutant model adjusting for NO_2 (1.13 [0.72, 1.76]; $r = 0.34-0.93$).

5.4.6 Severity of Asthma

There were no studies examining the association between long-term exposure to $PM_{10-2.5}$ and severity of asthma available for inclusion in the 2009 PM ISA (U.S. EPA, 2009). Recent studies are limited in number. In an epidemiologic study conducted in northern California, Balmes et al. (2014) examined the association between annual $PM_{10-2.5}$ and symptomatic asthma in a cross-sectional cohort study of adults with both asthma and allergies. The middle and highest tertiles of annual $PM_{10-2.5}$ exposure (10.68−12.68 and ≥12.71 $\mu g/m^3$, respectively) were not associated with increased odds of asthma symptoms compared to the lowest tertile of exposure (<10.68 $\mu g/m^3$).

Animal toxicological studies related to asthma severity are typically conducted in allergic animal models, which share phenotypic features with asthma (see Section 5.1.2.4). Inhalation exposure of rodents to $PM_{10-2.5}$ is technically difficult since rodents are obligatory nasal breathers. A group of recent studies examined the effects of long-term $PM_{10-2.5}$ using Asian sand dust and noninhalation routes of exposure (i.e., intra-tracheal instillation). Results provide biological plausibility for a potential role of $PM_{10-2.5}$ in enhancing allergic responses (Liu et al., 2014; He et al., 2013a; He et al., 2013b).

5.4.7 Subclinical Effects in Healthy Populations

Animal toxicological and epidemiologic studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations. As reported in the 2009 PM ISA (U.S. EPA, 2009), Dales et al. (2008) found a positive association between long-term exposure to $PM_{10-2.5}$ and eNO, a marker of inflammation, in an epidemiologic study among children living in Windsor, ON. In a recent animal toxicological study, Aztatzi-Aguilar et al. (2015) evaluated pulmonary oxidative stress and inflammatory responses in Sprague Dawley rats exposed for 8 weeks to $PM_{10-2.5}$ CAPs in Mexico City. A decrease in lung tissue heme oxygenase-1 activity was found ($p < 0.05$), but there was no change in γ-glutamyl cysteine synthetase catalytic subunit, another index of oxidative stress. Long-term exposure to $PM_{10-2.5}$ CAPs also resulted in a decrease in IL-6 protein ($p < 0.05$) and changes in the RAS. An increase in angiotensin receptor Type 1 protein was observed along with a decrease in its mRNA levels in lung tissue ($p < 0.05$). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. Protein and mRNA levels of angiotensin converting enzyme, which catalyzes the conversion of angiotensin I to angiotensin II, increased following long-term exposure to $PM_{10-2.5}$ CAPs ($p < 0.05$). Since deposition of inhaled $PM_{10-2.5}$ is expected to primarily occur in the extrathoracic airways (i.e., the nose) of rodents, this study links deposition in the nose to increased activity of the RAS and to a possible dampening of oxidative stress and inflammation in the lower airways. Additional study details are found in Table 5-38.

Table 5-38 Study-specific details from an animal toxicological study of long-term exposure to $PM_{10-2.5}$ and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley Age/Weight:	$PM_{10-2.5}$ CAPs Mexico City Particle size: $PM_{10-2.5}$ Control: Filtered air	Route: Inhalation Dose/Concentration: Coarse $PM_{10-2.5}$ 32 $\mu g/m^3$ Duration: Acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of RAS and kalikrein-kinin endocrine system • Heme oxygenase-1

IL-6 = interleukin 6; RAS = renin-angiotensin system.

5.4.8 Respiratory Mortality

Two recent European cohort studies evaluated the association between long-term $PM_{10-2.5}$ exposure and mortality and observed inconsistent results. In a pooled analysis of 22 cohorts from 13 European cohorts, Dimakopoulou et al. (2014) observed a null association with respiratory mortality in the ESCAPE cohort. In a French cohort, Bentayeb et al. (2015) observed a positive association between long-term $PM_{10-2.5}$ exposure and respiratory mortality. Both studies used statistical models to predict area-wide PM_{10} and $PM_{2.5}$ concentrations and used the subtraction method to estimate $PM_{10-2.5}$ concentrations, which contributes to uncertainty regarding exposure measurement error.

5.4.9 Summary and Causality Determination

Based on limited epidemiologic evidence demonstrating associations with some respiratory effects and a lack of evidence from experimental studies to support biological plausibility, the 2009 PM ISA (U.S. EPA, 2009) concluded that evidence was inadequate to assess the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects. The evidence characterizing the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects is detailed below (Table 5-39), using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015). A limited number of recent epidemiology studies expand the evidence base for decrements in lung function, the development of asthma, and respiratory infection in children. Uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding. An animal toxicological study examined the potential for inhalation of $PM_{10-2.5}$ to affect the respiratory

system and found upregulation of the RAS and a dampening of oxidative stress and inflammation in the lung. Several animal toxicological studies involving noninhalation routes of exposure found allergic inflammation and airway remodeling, which provides biological plausibility for the development of asthma. Overall, **the evidence is inadequate to infer the presence or absence of a causal relationship between long-term $PM_{10-2.5}$ exposure and respiratory effects.**

Table 5-39 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term $PM_{10-2.5}$ exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Limited epidemiologic evidence from multiple, high quality studies at relevant $PM_{10-2.5}$ concentrations	Decrements in attained lung function in children consistently observed in a limited number of cohort studies.	Gehring et al. (2013) Gehring et al. (2015a)	7.6–8.4 µg/m^3
	Increases in asthma incidence in children in a limited number of cohort studies. Supporting evidence from studies of asthma prevalence in children are inconsistent.	Gehring et al. (2015b) Gehring et al. (2015a)	8.4 µg/m^3
Coherence provided by epidemiologic studies of airway inflammation	Results from a single study show an association with eNO in children.	Dales et al. (2008)	7.3 µg/m^3
Uncertainty regarding confounding by copollutants	Potential copollutant confounding is not addressed.		
Uncertainty regarding exposure measurement error	Studies rely on subtraction method to estimate exposure to $PM_{10-2.5}$ adding uncertainty to the interpretation of effect estimates.	Section 3.3.1	
Biological plausibility	Evidence from a few animal toxicological studies involving intra-tracheal exposure provides biological plausibility for limited epidemiologic findings of the development of asthma.	Section 5.4.1	
Limited evidence from a toxicological study at relevant concentrations	Results from a single inhalation study in rodents show respiratory effects.	Aztatzi-Aguilar et al. (2015)	32 µg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

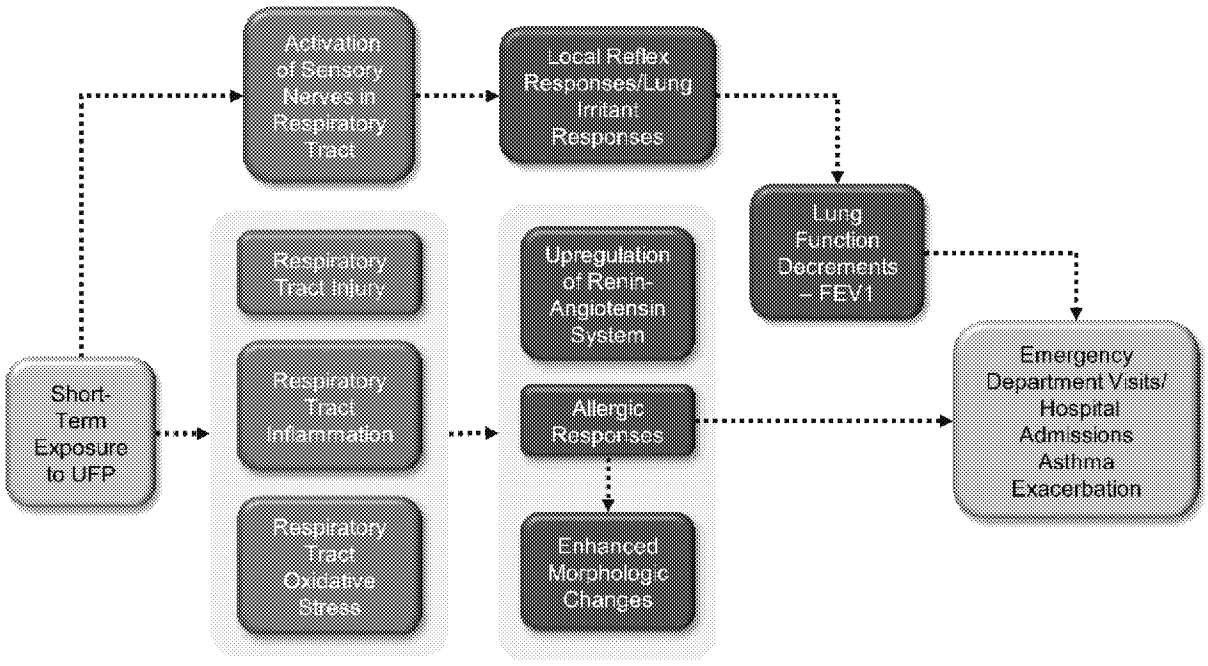
5.5 Short-Term UFP Exposure and Respiratory Effects

The 2009 PM ISA concluded that the relationship between short-term exposure to UFP and respiratory effects is "suggestive of a causal relationship" (U.S. EPA, 2009). This conclusion was based on limited, but supporting, epidemiologic evidence indicating associations with hospital admissions or ED visits for respiratory-related diseases, respiratory infection, and asthma exacerbation. Also providing support, personal ambient UFP exposure from time spent in high- and low-traffic areas was associated with lung function decrements in adults with asthma. The few available experimental studies provided limited coherence with epidemiologic findings for asthma exacerbation. Experimental studies of healthy human subjects and animals were also limited in number. Despite some evidence indicating a relationship between UFP exposure and respiratory effects, there was substantial uncertainty due to the small evidence base, a heterogeneous array of respiratory endpoints examined, indeterminate adequacy of UFP measurements, and limited biological plausibility.

For many respiratory outcomes, recent studies have not changed the overall evidence base. For asthma exacerbation, there continues to be some epidemiologic evidence, which is not entirely consistent, as well as some animal toxicological evidence (Section 5.5.2). Epidemiologic evidence continues to be consistent for respiratory-related diseases (Section 5.5.5) and inconsistent for COPD exacerbation (Section 5.5.3). Unlike findings reported in the 2009 PM ISA (U.S. EPA, 2009), recent findings are inconsistent for respiratory infection (Section 5.5.4). Recent experimental findings in healthy populations and animal models of cardiovascular disease show that short-term UFP exposure affects some respiratory responses in rodents (Section 0 and Section 5.5.7). Epidemiologic findings in healthy populations are inconsistent, including those for personal ambient exposures (Section 0). Evidence for respiratory mortality is limited (Section 5.5.8). Information on confounding by traffic-related copollutants continues to be limited, and inference about an independent effect of UFP exposure is limited because of uncertainty in the representativeness of UFP measurements, assessed mostly at fixed-site monitors.

5.5.1 Biological Plausibility

This section describes biological pathways that potentially underlie respiratory effects resulting from short-term exposure to UFP. Figure 5-49 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" short-term exposure to UFP may lead to respiratory effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.5.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-49 Potential biological pathways for respiratory effects following short-term UFP exposure.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Although all size fractions of PM may contribute to oxidative stress, UFPs may contribute disproportionately more as a function of their mass due to their large surface/volume ratio. The relative enrichment of redox active surface components, such as metals and organics, per unit mass may translate

to a relatively greater oxidative potential of UFPs compared with larger particles with similar surface components. In addition, the greater surface per unit volume may deliver relatively more adsorbed soluble components to cells. These components may undergo intra-cellular redox cycling following cellular uptake. Furthermore, per unit mass, UFPs may have more opportunity to interact with cell surfaces due to their greater surface area and their greater particle number compared with larger PM. These interactions with cell surfaces may lead to ROS generation, as described in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). Recent studies have also demonstrated that UFPs have the capacity to cross cellular membranes by nonendocytic mechanisms involving adhesive interactions and diffusion, as described in CHAPTER 4. This may allow UFPs to interact with or penetrate intra-cellular organelles.

Evidence that short-term exposure to UFP may affect the respiratory tract generally informs two proposed pathways (Figure 5-49). The first pathway begins with injury, inflammation, and oxidative stress responses, which are difficult to disentangle. Inflammation generally occurs as a consequence of injury and oxidative stress, but it may also lead to further oxidative stress and injury due to secondary production of ROS by inflammatory cells. The second pathway begins with the activation of sensory nerves in the respiratory tract that can trigger local reflex responses and transmit signals to regions of the central nervous system that regulate autonomic outflow.

Injury, Inflammation, and Oxidative Stress

Experimental evidence that short-term exposure to UFP affects the respiratory tract is provided by numerous studies and supports a role for injury, inflammation, and oxidative stress. A few studies demonstrate markers of injury (i.e., decreased CC16 protein) and oxidative stress (4-hydroxynoneal, 3-nitrotyrosine, Ym1) (Cheng et al., 2016; Li et al., 2010; Kooter et al., 2006). Seagrave et al. (2008) exposed rats to GE containing UFP and found increased lung tissue chemiluminescence that was not present when GE was filtered, indicating that the particulate fraction played a role in the oxidative stress response. In the study by Cheng et al. (2016), a time-course analysis demonstrated oxidative stress in olfactory epithelium after a single exposure of 5 hours, as well as after multiple exposures over 3 weeks. Inflammatory responses were seen in some studies (Cheng et al., 2016; Aztatzi-Aguilar et al., 2015), but not others (Tyler et al., 2016; Amatullah et al., 2012). In Tyler et al. (2016), evidence for inflammation was found in a model of cardiovascular disease but not in healthy animals. In Cheng et al. (2016), time course analysis showed that inflammatory responses occurred concomitantly with oxidative stress responses.

Inflammation was not seen in human subjects with asthma following short-term exposure to UFP (Gong et al., 2008). However, supportive evidence for enhancement of allergic responses is provided by a study in human subjects with allergic asthma who were exposed to ultrafine carbon (Schaumann et al., 2014). Enhancement of allergic responses was also found in two studies in animals (Li et al., 2010; Kleinman et al., 2005). In Li et al. (2010), intra-nasal cosensitization with OVA and UFP was required for exacerbation of responses to inhaled UFP and OVA. These responses included increased BALF

eosinophils and neutrophils, upregulation of Th2 and Th17 cytokines, increased plasma OVA-specific IgE, and enhanced morphologic changes that extended to more distal parts of the lung. These results are consistent with some epidemiologic evidence of asthma-related hospital admissions and ED in association with UFP concentrations (Section 5.5.2.1).

Activation of Sensory Nerves

Short-term exposure to UFP did not alter pulmonary function in animal studies (Amatullah et al., 2012; Seagrave et al., 2008). However, in human subjects with asthma, decreases in FEV_1 and oxygen saturation were observed (Gong et al., 2008). Although lung irritant responses can sometimes result in decreased FEV_1, it is not clear whether inhalation of $PM_{2.5}$ led to FEV_1 changes by this pathway or whether it was mediated by inflammation. Epidemiologic panel studies conducted in people with asthma also found associations with lung function decrements (Mirabelli et al., 2015; McCreanor et al., 2007). These results are also consistent with some epidemiologic evidence of asthma-related hospital admissions and ED in association with UFP concentrations (Section 5.5.2.1).

Another study found upregulation of the RAS, as indicated by an increase in mRNA for angiotensin receptor Type 1 and angiotensin converting enzyme, in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study.

Summary

As described here, there are two proposed pathways by which short-term UFP exposure may lead to respiratory health effects. One pathway involves respiratory tract inflammation and allergic responses, which are linked to asthma exacerbation. The second pathway involves the activation of sensory nerves in the respiratory tract leading to lung function decrements, which are also linked to asthma exacerbation. While experimental studies involving animals or human subjects contribute most of the evidence of upstream effects, epidemiologic studies found associations between short-term UFP exposure and lung function decrements. Together, these proposed pathways provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.5.9).

5.5.2 Asthma Exacerbation

In the 2009 PM ISA (U.S. EPA, 2009), the evaluation of the relationship between short-term UFP exposure and asthma exacerbation consisted of a limited number of epidemiologic, controlled human exposure, and animal toxicological studies. Epidemiologic studies provided some evidence of an association between short-term UFP exposure and asthma exacerbation. Evidence for decrements in pulmonary function was found in subjects with asthma in the controlled human exposure study. Evidence for enhanced allergic responses was found in the animal toxicological study in a model of allergic airway disease that shares phenotypic features with asthma.

5.5.2.1 Epidemiologic Studies

In the 2009 PM ISA (U.S. EPA, 2009), studies of hospital admissions, ED visits (Andersen et al., 2008b; Halonen et al., 2008), and physician visits (Sinclair and Tolsma, 2004) reported evidence of associations across a range of lags, as well as for different UFP concentration metrics (i.e., number concentration [NC] and surface area [SA]). In panel studies of asthma symptoms in adults with asthma, supporting evidence of asthma exacerbation was observed across size fractions from $NC_{10–100}$ nm to $NC_{500–2,500}$ nm (Mar et al., 2004; von Klot et al., 2002). Supporting evidence was also provided by a study of lung function in adults with asthma in which $NC_{10–100}$ nm was associated with decrements in FEV_1, FVC, $FEF_{25–75\%}$, but not with increases in eNO after walking on a high-traffic road or in a park (McCreanor et al., 2007). This study of scripted exposure minimized uncertainty in the UFP exposure metric by measuring personal ambient UFP at the site of exposure. The evidence across studies was not entirely consistent, as associations between UFP exposure and ED visits for asthma were not observed in the Atlanta-based SOPHIA study (Peel et al., 2005). Additionally, the overall interpretation of results from epidemiologic studies that examined UFP exposures, including those focusing on asthma exacerbation, is complicated by the spatial variability in UFP concentrations, the correlation between UFPs and other traffic-related pollutants, and the various size fractions and concentration metrics used as UFP exposure surrogates.

A few recent epidemiologic studies add to those from the 2009 PM ISA (U.S. EPA, 2009) and continue to provide some, but not entirely consistent, support for associations between increases in short-term UFP concentrations exposure and asthma exacerbation. The supporting evidence comes from an array of outcomes related to asthma exacerbation, including hospital admissions, ED visits, and physician visits for asthma to asthma symptoms and medication use. Additional evidence from studies in adults with asthma using personal ambient UFP exposures via scripted exposures in high-traffic locations is more consistent for lung function decrements than pulmonary inflammation. The relatively small body of recent studies of asthma hospital admissions, ED visits, and physician visits examined a range of UFP size fractions, which complicates the interpretation of results across studies. Several studies examined $NC_{10–100}$ nm exposure among older children (>3 years), in whom the ascertainment of asthma is more

reliable. All the recent studies used NC to represent UFP exposure; and as detailed in the Preface , when examining the size distribution of particles 67 to 90% of NC contains particles <0.1 μm. Samoli et al. (2016a) reported no association with asthma hospital admissions in a study of five European cities. In contrast, Iskandar et al. (2012) reported an association with NC_{10-700} nm in a study conducted in Copenhagen, Denmark. Across studies, a similar array of lags was examined and no particular lag was identified as having a stronger association with asthma hospital admissions, but many results support associations with UFP concentrations with a lag of 1 to 5 days or averaged over 3 to 6 days (Table 5-40). While the examination of the relationship between short-term UFP exposure and asthma hospital admissions focused on studies that examined daily changes in UFP concentrations and hospital admissions (e.g., time-series, case-crossover analyses), the assessment of the relationship with ED visits was limited to a study that focused on asthma exacerbations that led to an ED visit (Evans et al., 2014). In a group of children with asthma enrolled in the School-Based Asthma Therapy trial, Evans et al. (2014) examined whether exposure to traffic-related pollutants, including UFPs, resulted in an asthma exacerbation that lead to an ED visit over multiday averages up to 0−7 days. There was some evidence of an association for lag 0−3 days (OR = 1.3 [95% CI: 0.90, 1.8] for a 2,088 increase in UFPs per cm^{-3}); however, the association was more evident in children receiving preventative medication at school compared to at home. A recent study examined the association between UFP exposure and lung function and subclinical effects in adults with asthma. In this panel study of 18 adults in Atlanta, GA, NC_{total} was associated with increased eNO and decreased FEV_1 (Mirabelli et al., 2015). Personal NC_{total} was measured during two morning commutes through rush-hour traffic, resulting in higher exposure levels. The observed associations with FEV_1 were consistent across spirometry test conducted 0, 1, 2, and 3 hours post-commute, while increased eNO was only associated with UFP exposure in adults with below-median asthma control.

Table 5-40 Epidemiologic studies of UFP and asthma hospital admissions, emergency department (ED) visits, and physician visits.

Study, Location, Years, Age Range	Exposure Assessment	UFP Concentration (particles/cm^3)[a]	Single Pollutant Effect Estimate (95% CI)	Copollutant Examination
Hospital admissions				
Andersen et al. (2008b) Copenhagen, Denmark 2001–2004 5–18 yr	$NC_{10–100}$ nm, NC total and NC with median diameters 12, 23, 57, 212 nm One monitor, within 15 km of hospitals, mean 6 km. *r* for NC_{total} = 0.62 with roadside monitor 3 km away, 0.80 with rural monitor	$NC_{10–100}$ nm Mean: 6,847 99th: 16,189 NC_{total} Mean: 8,116 99th: 19,895	RR per 3,259 Lag 0–4 $NC_{10–100}$ nm 1.06 (0.97, 1.16) RR per 3,907 NC_{total} 1.07 (0.98, 1.17)	Correlation (*r*): 0.61 NO_2, 0.48 CO, 0.40 $PM_{2.5}$ Copollutant models with: NO_2, CO
†Iskandar et al. (2012) Copenhagen, Denmark 2001–2008 0–18 yr	$NC_{10–700}$ nm One monitor, within 15 km of hospitals, mean 6 km	Mean: 6,398 75th: 7,951	OR per 7,004 Lag 0–4 1.06 (0.98, 1.14)	Correlation (*r*): 0.51 NO_2, 0.45 NO_X, 0.26 $PM_{2.5}$ Copollutant models with: NO_2, NO_X, $PM_{2.5}$
†Samoli et al. (2016a) Five European cities 2001–2011 All ages	Barcelona: $NC_{5–1,000}$ nm Copenhagen: $NC_{6–700}$ nm Helsinki: $NC_{10–100}$ nm Rome and Stockholm: $NC_{7–3,000}$ nm One or two sites per city. All urban background sites except for traffic site in Rome	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	Percent increase per 10,000 Lag 1 2.1 (−0.28, 4.6)	Correlation (*r*): 0.38–0.69 NO_2, 0.07–0.67 CO, 0.09–0.57 $PM_{2.5}$ Copollutant models with: NR

Table 5-40 (Continued): Epidemiologic studies of ultrafine particle (UFP) and asthma hospital admissions, emergency department (ED) visits, and physician visits.

Study, Location, Years, Age Range	Exposure Assessment	UFP Concentration (particles/cm^3)[a]	Single Pollutant Effect Estimate (95% CI)	Copollutant Examination
ED visits				
Peel et al. (2005) Atlanta, GA 1998–2000 All ages	$NC_{10–100}$ nm 1 monitor, near city center	Mean: 38,000 90th: 74,600	RR per 30,000 Lag 0–2 1.00 (0.98, 1.02)	Correlation (*r*): NR Copollutant models with: NR
†Evans et al. (2014) Rochester, NY 2006–2009 3–10 yr	$NC_{10–100}$ nm 1 monitor 1.6–11 km from school, within 15 km of home, 1.5 km of highway.	Mean: 5,151 75th: 6,449 95th: 9,575	OR per 2,008 Lag 0–3 1.27 (0.90, 1.79)	Correlation (*r*): Warm season = 0.57 O_3 Copollutant models with: CO, O_3
Physician visits				
Sinclair and Tolsma (2004) Atlanta, GA 1998–2000 All ages	$SC_{10–100}$ nm 1 monitor, near city center	Mean: 249 μm^2/cm^2	RR per 244 Lag 3–5 1.22 (95 CI NR)	Correlation (*r*): NR Copollutant models with: NR

CO = carbon monoxide, CI = confidence interval, NC = number concentration, NO_2 = nitrogen dioxide, NO_X = sum of NO_2 and nitric oxide, NR = not reported, O_3 = ozone, OR = odds ratio, RR = relative risk, SC = surface area concentration, SD = standard deviation, SO_2 = sulfur dioxide, UFP = ultrafine particles.

[a]All data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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The epidemiologic studies of short-term exposure to UFP and asthma hospital admissions each have 1 to 2 monitors per study, covering a 15-km radius in some cases (Table 5-40). Spatial variability in UFP concentration may not be captured over this area, introducing some uncertainty in the exposure surrogate (Section 2.5; Section 3.4.2.2). It is possible that associations are related to similarities in temporal variability of UFP sources throughout study areas, as Sarnat et al. (2010) observed for spatially-variable NO_2, but this remains an uncertainty since spatiotemporal variability across cities has not been well characterized. In addition to major uncertainties regarding the spatial variability in UFP and the various size fractions and concentration metrics used as UFP exposure surrogates, confounding by traffic-related pollutants also remains a concern, as studies have not thoroughly examined potential copollutant confounding. Studies evaluated in the 2009 PM ISA (U.S. EPA, 2009), which focused on both asthma hospital admissions (Andersen et al., 2008b) and lung function changes (McCreanor et al., 2007) in people with asthma, provided initial evidence that UFP associations persisted after adjustment for NO_2 or CO even when UFP was moderately correlated with copollutants [e.g., $r = 0.58$ for personal ambient UFP and NO_2 exposures (McCreanor et al., 2007)]. Recent results show robust UFP associations to adjustment for CO and O_3, but null associations with adjustment for NO_2 or NO_X (Table 5-40).

5.5.2.2 Controlled Human Exposure

Only one study evaluated in the 2009 PM ISA (U.S. EPA, 2009) investigated the effects of short-term UFP exposure and respiratory effects in individuals with asthma. In this study, Gong et al. (2008) reported decreases in pulmonary function (oxygen saturation and FEV_1) following a 2-hour exposure to 100 $\mu g/m^3$ UFP CAPs (less than 0.18 μm aerodynamic diameter). No changes in pulmonary inflammation were found.

5.5.2.3 Animal Toxicological Studies

As described in the 2009 ISA for PM (U.S. EPA, 2009), Kleinman et al. (2005) found that a multiday exposure to roadway ultrafine PM (UFP) CAPs in Los Angeles enhanced allergic responses in OVA-sensitized and challenged BALB/c mice, and that this effect was dependent on proximity to the PM source. Recently, Li et al. (2010) extended these observations in OVA-sensitized and challenged BALB/c mice. A hybrid exposure to Los Angeles UFP CAPs was conducted by intra-nasal cosensitization with OVA and UFP (Days 1, 2, and 4), followed 2 weeks later with inhalation exposures to concentrated UFP (Days 18, 19, 22, 23 and 24) that overlapped with intra-nasal OVA challenge (Days 23 and 24). Only mice that were cosensitized with UFP responded to secondary OVA challenges with increases in lavaged eosinophils, plasma OVA-specific IgE, and pulmonary expression of eotaxin, IL-5, IL-13, and Muc5ac ($p < 0.05$). Inhalation exposure to UFP during the challenge phase enhanced these allergic responses compared to filtered air exposed mice ($p < 0.05$). Similarly, UFP exposure during OVA challenge

enhanced neutrophil influx and pulmonary expression of IL-17 and Ym1, a marker of oxidative stress, in mice which were cosensitized with UFP and OVA ($p < 0.05$). These results demonstrate that short-term UFP exposure exacerbated the effects of allergen and suggest the involvement of Th2 and Th17 helper cells in the response. Pulmonary histopathology revealed that UFP inhalation during the OVA challenge extended allergic inflammation to more distal regions of the lung (i.e., the proximal alveolar duct and adjacent alveolar parenchyma). Their small size may have allowed UFPs to evade phagocytosis and deposit in the deep lung due to diffusion, as well as to stick to the airways walls due to Van der Waal's forces. The oxidative potential of urban UFP (Li et al., 2009) may have also contributed to inflammatory responses. It should be noted that in the recent study by Li et al. (2010) PM and allergens were coinstilled during sensitization prior to the inhalation challenge. This study design more clearly demonstrates the exacerbation of allergic responses than adjuvant activity. Short-term exposure to UFP may also promote allergic sensitization and additional experiments employing different study designs are needed to show this effect. Additional study details are found in Table 5-41.

Table 5-41 Study-specific details from an animal toxicological study of short-term exposure to UFP and subclinical effects underlying asthma exacerbation in a model of allergic airway disease.

Study/Study Population	Pollutant	Exposure	Endpoints
Li et al. (2010) Species: Mouse Sex: Female Strain: BALB/c Age/Weight: 8–10 weeks	Ultrafine—ambient Los Angeles OVA Particle size: <0.18 µm Particle mass: 101.3 ± 5.1 µg/m^3	Route: Intra-nasal sensitization with PM and OVA (2 days) Inhalation of PM on days of OVA challenge Dose/Concentration: 4 h/day for 5 days	PM characterization Serum IgE, IgG1 BALF cells BALF cytokines Histopathology—lung

IgE = immunoglobulin E; IgG1 = immunoglobulin G1; BALF = bronchoalveolar lavage fluid; OVA = ovalbumin.

5.5.3 Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

The 2009 PM ISA (U.S. EPA, 2009) evaluated a small body of literature examining the association between UFP and hospital admissions and ED visits for COPD. The studies evaluated in the 2009 PM ISA, limited to single-cities, provided inconsistent evidence of associations with UFPs. There are a few recent studies of UFP exposure and COPD exacerbation, but the evidence base remains small and does not clearly support a relationship. This applies to COPD hospital admissions and ED visits (Table 5-42), which can result from uncontrollable respiratory symptoms that are hallmarks of COPD

exacerbation such as cough, sputum production, and shortness of breath. The uncertain adequacy of the UFP concentration metrics used for exposure surrogates is a major limitation in the evidence base overall.

Recently, some studies examined associations with COPD, but they are limited to studies of hospital admissions and again are conducted in individual cities. Recent studies examine COPD hospital admissions in Europe and observe an association in Rome, Italy (Belleudi et al., 2010) but not a multicity study that includes Rome (Samoli et al., 2016a) (Table 5-42). UFP concentrations were averaged over 24 hours, and all studies examined an array of lags (up to 10 days). In Rome, Italy, (Belleudi et al., 2010) found evidence of a positive association between UFP and COPD hospital admissions at 0−1-day distributed lag among adults aged 35 years and older (0.95 [95% CI: −0.8, 2.73]). Adjustment for PM_{10} or for $PM_{2.5}$ did not alter the association of COPD (lag 0) with particle NC (1.9% [95% CI: 0.1, 3.8] and 1.3% [95% CI: 0.8, 3.5%], per 10,000 particles/cm^3, respectively). There was some evidence that associations were stronger in terms of magnitude and precision in the spring and fall season (3.72% [95% CI: 0.81, 6.70]). Additionally, in a study conducted in Helsinki, Finland, Halonen et al. (2009b) reported an association between COPD hospital admissions in the nucleation mode (<0.03 μm), with an 0.8% (95% CI: −2.28, 3.97) increase in hospital admissions for a 3,583-count increase in the nucleation mode, and a 0.82% (95% CI: −1.51, 3.20) increase in hospital admissions for a 2,467-count increase in the Aitken mode (0.03−0.1 μm) (lag 3). Among adults with COPD in Erfurt, Germany, NC_{10-100} nm was not associated with blood levels of the proinflammatory cells neutrophils and eosinophils or most markers of blood coagulation that are linked to cardiovascular effects rather than COPD (Bruske et al., 2010; Hildebrandt et al., 2009).

Epidemiologic studies examining respiratory infection are limited by their UFP exposure assessment, because they relied on data from one or two monitors and thus could not capture the spatial variability in UFP concentrations across study locations (Section 2.5.1, Section 3.4.2.2). Additionally, the limited assessment of potential copollutant confounding complicates the interpretation of results and understanding whether UFPs are independently associated with COPD exacerbations or may be serving as an indicator of highly correlated copollutants.

Table 5-42 Epidemiologic studies of UFP and exacerbation of chronic obstructive pulmonary disease.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration particles/cm^{3a}	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998–2000	NC_{10-100} nm One monitor, near city center	ED visits All ages Visits concentrated in city center	Mean: 38,000 SD: 40,700 90th: 74,600	RR per 30,000 Lag 0–2 0.98 (0.94, 1.02)	No copollutant model Copollutant correlations NR
†Belleudi et al. (2010) Rome, Italy 2001–2005	NC_{total} Condensation Particle Counter One monitor, 2 km from city center	Hospital admissions Adults ≥35 yr	Mean: 37,456 SD: 21,394 75th: 47,995	RR per 9,392 Lag 0 1.02 (1.00, 1.03)	No copollutant model No copollutants examined r = 0.55 $PM_{2.5}$.
†Samoli et al. (2016a) Barcelona, Spain; Copenhagen, Denmark; Helsinki, Finland; Rome, Italy; Stockholm, Sweden 2001–2011 across cities	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome and Stockholm: $NC_{7-3,000}$ nm One or two sites per city. All urban background sites except for traffic site in Rome	Hospital admissions All ages	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	RR per 10,000 Lag 0 0.99 (0.96, 1.02)	No copollutant model r = 0.38–0.69 NO_2, 0.07–0.67 CO, 0.09–0.57 $PM_{2.5}$.

CO = carbon monoxide, CI = confidence interval, ED = emergency department, NC = number concentration, NO_2 = nitrogen dioxide, NR = not reported, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, r = correlation coefficient, RR = relative risk, SD = standard deviation, ultrafine particles.

aAll data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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5.5.4 Respiratory Infection

Regarding the association between UFP and hospital admissions/ED visits for respiratory infections, the body of literature reviewed in the 2009 PM ISA (U.S. EPA, 2009) was very small and provided no evidence of associations with respiratory infections and was limited to single-city studies. Consistent with the 2009 PM ISA, recent studies are limited in number and focus on examining associations between short-term UFP exposure and respiratory infections in individual cities. In Rome, Italy, Belleudi et al. (2010) found no evidence of an association between UFP (UFPs were measures using particle NC from a single monitor) and lower respiratory tract infection hospital admissions at any lag among adults aged 35 years and older. The effect was positive, but imprecise at lag 2 and lag 3 (0.19% [95% CI: −1.48, 1.90] and 0.29% [95% CI: −1.37, 1.98], per 10,000 particles/cm^3, respectively). In a study of UFPs and respiratory hospital admissions in five European cities in 2001−2011, Samoli et al. (2016a) found no overall association using city-specific estimates to obtain pooled estimates but did identify a positive association with hospital admissions during warm months of April−September of 4.27% (95% CI 1.68−6.92) for an increase in 10,000 particles/cm^3 (lag 2). This effect estimate was robust to inclusion of CO and NO_2 in the statistical model. Halonen et al. (2009b), in a study conducted in Helsinki, Finland, reported no associations for pneumonia hospital admissions in the nucleation mode (<0.03 μm), but observed a 1.5% (95% CI: −0.72, 3.77) increase in hospital admissions for a 2,467-count increase in the Aitken mode (0.03−0.1 μm) (lag 3). Some similarity of the effect estimates was expected by the authors due to the high correlation between these particle fractions.

The body of literature that studied the association between UFPs and hospital admissions/ED visits for respiratory infection hospital admissions expanded since the 2009 PM ISA (U.S. EPA, 2009) but remains somewhat limited. The available evidence suggests small associations between UFPs and respiratory infections, though the distinct size fractions under analysis in each study make cross-study comparisons difficult. The limited evidence from previous and recent studies does not clearly link short-term UFP exposure to increases in respiratory infection, based largely on hospital admissions, ED visits, and physician visits for URI, pneumonia, or LRI, which combines pneumonia and bronchitis (Table 5-43). There is little information to assess the biological plausibility for the supporting findings. Host defense mechanisms that protect the respiratory tract from pathogens such as mucociliary clearance, alveolar macrophage clearance, or innate and adaptive immunity were not assessed in relation to short-term UFP exposure. For the supporting evidence, information also is lacking on sources of heterogeneity, C-R, and the influence of other traffic-related pollutants.

Table 5-43 Epidemiologic studies of UFP and respiratory infection.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration Particles/cm^{3a}	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
Peel et al. (2005) Atlanta, GA 1998–2000	NC_{10-100} nm One monitor, near city center	ED visits URI and pneumonia All ages Visits concentrated in city center	Mean: 38,000 SD: 40,700 90th: 74,600	RR per 30,000 Lag 0–2 URI 0.99 (0.97, 1.01) Pneumonia 0.98 (0.95, 1.00)	No copollutant model Copollutant correlations NR
Sinclair et al. (2010) Atlanta, GA 1998–2000	SC_{10-100} nm One monitor, near city center	Physician visits URI and LRI All ages HMOs in city outskirt	Mean: 249 $\mu m^2/cm^2$ SD: 244	RR per 244 URI, Lag 3–5 1.04 (95% CI NR) LRI, Lag 0–2 1.10 (95% CI NR)	No copollutant model Copollutant correlations NR
Halonen et al. (2009b) Helsinki, Finland 1998–2004	NC_{30-100} nm One monitor	Hospital admissions Pneumonia Older adults	Median: 3,628 IQR: 1,309 75th: 4,937	RR per 1,309 Lag 0–4 1.04 (1.00, 1.08)	No copollutant model r = 0.48 $PM_{2.5}$, 0.65 NO_2, 0.41 CO, 0.72 traffic $PM_{2.5}$
†Belleudi et al. (2010) Rome, Italy 2001–2005	NC_{total} One monitor, 2 km from city center	Hospital admissions LRI Adults ≥35 yr	Mean: 37,456 SD: 21,394 75th: 47,995	RR per 9,392 Age 35–74 yr, lag 0 1.03 (1.00, 1.07)	No copollutant model r = 0.55 $PM_{2.5}$.

Table 5-43 (Continued): Epidemiologic studies of ultrafine particle (UFP) and respiratory infection.

Study	Exposure Assessment	Outcome Assessment	UFP Concentration Particles/cm^{3}[a]	Single Pollutant Effect Estimate 95% CI	UFP Copollutant Model Results and Correlations
†Samoli et al. (2016a) Barcelona, Spain; Copenhagen, Denmark; Helsinki, Finland; Rome, Italy; Stockholm, Sweden 2001–2011 across cities	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome/Stockholm: $NC_{7-3,000}$ nm One or two monitors per city	Hospital admissions LRI All ages	Means Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	RR per 10,000 Lag 1 0.99 (0.98, 1.01)	No copollutant model r = 0.38–0.69 NO_2, 0.07–0.67 CO, 0.09–0.57 $PM_{2.5}$.

CO = carbon monoxide, CI = confidence interval, ED = emergency department, HMO = health maintenance organization, LRI = lower respiratory infection, NC = number concentration, NO_2 = nitrogen dioxide, NR = not reported, $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter ≤2.5 µm, r = correlation coefficient, RR = relative risk, SD = standard deviation, UFP = ultrafine particles, URI = upper respiratory infection.

[a]All data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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5.5.5 Combinations of Respiratory-Related Hospital Admissions and Emergency Department (ED) Visits

The evidence more consistently links increases in UFP concentration to increases in respiratory-related diseases broadly than to asthma, COPD, or respiratory infections. Recent findings not only add consistency for hospital admissions or ED visits, but they also indicate lung function changes among adults with asthma or COPD. As is observed with asthma exacerbation (Section 5.5.2), distinguishing an association for UFP and respiratory-related diseases independent of NO_2 remains uncertain. As noted previously, studies of respiratory-related diseases examine either all respiratory-related diseases or only a subset, which can complicate the interpretation of results across studies.

There is considerable variation across studies in the size fractions examined and, in the fraction, most strongly associated with hospital admissions and ED visits for respiratory-related diseases (Table 5-44). Associations were consistently observed for NC up to 100 nm (Lanzinger et al., 2016b; Samoli et al., 2016b; Leitte et al., 2011; Andersen et al., 2008b; Halonen et al., 2008). In Beijing, China, associations were observed with UFP NC and SC (Leitte et al., 2011). Results also are consistent with NC with an upper bound that included larger particles (Table 5-44); however, as detailed in CHAPTER 1, it has been demonstrated that 67−90% of NC represents particles <0.1 μm although the upper bound of the UFP size distribution measured by NC may include larger size particles. In contrast, hospital admissions and ED visits for respiratory-related diseases are inconsistently associated with size fractions with upper bounds less than 50 nm (Leitte et al., 2011; Halonen et al., 2008).

A few recent epidemiologic studies focusing on individuals with a combination of respiratory-related diseases that also examined associations with UFP concentrations provide evidence that supports an association with respiratory-related hospital admissions and ED visits. For adults with asthma and COPD in four European cities (Helsinki, Finland; Athens, Greece; Amsterdam, the Netherlands; Birmingham, U.K.), NC_{total} measured outside the home but not at a monitor in the city was associated with lung function decrements (de Hartog et al., 2010). Additionally, within the UFIREG study, within Augsberg, Germany, NC_{total} was found to be highly correlated across four traffic and nontraffic sites (r = 0.77−0.95) (Lanzinger et al., 2016b; Cyrys et al., 2008).

Table 5-44 Epidemiologic studies of UFP and respiratory-related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	Mean UFP Concentration Particles/cm^{3}[a]	Single Pollutant Effect Estimate 95% CI	Copollutant Examination
Hospital admissions				
†Samoli et al. (2016a) Five European cities 2001–2011 All ages	Barcelona: $NC_{5-1,000}$ nm Copenhagen: NC_{6-700} nm Helsinki: NC_{10-100} nm Rome/Stockholm: $NC_{7-3,000}$ nm One or two monitors per city	Barcelona: 19,554 Copenhagen: 5,105 Helsinki: 7,951 Rome: 34,043 Stockholm: 9,128	(ICD9: 466, 480–487; 490–492, 494, 496; 493) Percent increase per 10,000, lag 5 0.43 (−0.58, 1.45)	Correlation (*r*): 0.38–0.69 NO_2, 0.07–0.67 CO, 0.09–0.57 $PM_{2.5}$ Copollutant models with: NO_2, CO
†Samoli et al. (2016b) London, U.K. 2011–2012 ≥65 yr	Regional nucleation (nuc) factor 20 nm peak, road traffic factor 30 nm mode, urban background (BG) factor 70 nm peak, long-range transport factor 250 nm mode One monitor	Median Regional nuc: 280 Road traffic: 2,355 Urban BG: 1,893 Long-range transport: 105	(ICD10: J00–J99) RR per IQR, lag 2 Regional nuc: 0.99 (0.98, 1.00) Road traffic: 0.99 (0.97, 1.00) Warm season Urban BG: 1.02 (1.00, 1.04) Long-range: 1.01 (1.00, 1.03)	Correlation (*r*): NR Copollutant models with: NR
†Lanzinger et al. (2016b) Five European cities (UFIREG) 2011–2014 across cities All ages	NC_{20-100} nm, NC_{20-800} nm One monitor Prague, number of monitors NR in other cities	NC_{20-100} nm, NC_{20-800} nm Augsburg: 5,880, 7,239 Chernivtsi: 5,511, 7,775 Dresden: 4,286, 5,851 Ljubljana: 4,693, 6,750 Prague: 4,197, 5,799	(ICD10: J00–J99) Percent increase per 2,750, Lag 2–5 NC_{20-100} nm: 2.2 (−0.9, 5.3) Percent increase per 3,675, Lag 2–5 NC_{20-800} nm: 3.1 (−0.1, 6.5)	Correlation (*r*): 0.51 and 0.33 NO_2, 0.37 and 0.30 $PM_{2.5}$ (Augsburg and Dresden) Copollutant models with: NO_2

Table 5-44 (Continued): Epidemiologic studies of ultrafine particle (UFP) and respiratory related hospital admissions and emergency department (ED) visits.

Study, Location, Years, Age Range	Exposure Assessment	Mean UFP Concentration Particles/cm^{3a}	Single Pollutant Effect Estimate 95% CI	Copollutant Examination
ED visits				
†Leitte et al. (2011) Beijing, China 2004–2006 All ages	NC_{10-30} nm, NC_{30-50} nm, NC_{50-100} nm, NC_{total} SC_{50-100} nm One monitor	NC_{10-30} nm: 6,900 NC_{30-50} nm: 4,900 NC_{50-100} nm: 6,700 UFP (<100 nm): 22,000 NC_{total}: 29,000 SC_{50-100} nm: 110	(J00–J99) RR, lag 0 NC_{10-30} nm, per 4,300 0.98 (0.93, 1.04) NC_{30-50} nm, per 2,300 1.03 (0.99, 1.08) NC_{50-100} nm, per 3,600 1.03 (0.99, 1.07) UFP, per 11,000 1.01 (0.95, 1.07) NC_{total}, per 12,600 1.03 (0.98, 1.09) SC_{50-100} nm, per 60 1.03 (0.99, 1.07)	Correlation (*r*): With NO_2: −0.16 NC_{3-10} nm, −0.09 NC_{10-30} nm, 0.22 NC_{30-50} nm, 0.43 NC_{50-100} nm, 0.27 NC_{total}, 0.45 SC_{50-100} nm Copollutant models with: NO_2

CO = carbon monoxide, COPD = chronic obstructive pulmonary disease, CI = confidence interval, LRI = lower respiratory infection, NC = number concentration, NO_2 = nitrogen dioxide, NR = not reported, RR = relative risk, SC = surface concentration, SD = standard deviation, SO_2 = sulfur dioxide, UFIREG = Ultrafine particles—an evidence-based contribution to the development of regional and European environmental and health policy; UFP = ultrafine particles.

[a]All data are for 24-hour average.

†Studies published since the 2009 PM ISA.

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Recent results from copollutant models provide additional indication that adjustment for NO_2 or CO has varying effect on UFP associations with respiratory-related diseases. Associations for NC with upper bounds of 100 nm are sometimes attenuated with adjustment for NO_2 (Lanzinger et al., 2016b; Leitte et al., 2011). Other results are for larger sized NC with upper bounds ranging from 290–3,000 nm, with many showing that associations persist with adjustment for NO_2 or CO (Samoli et al., 2016a; Halonen et al., 2009b) and some showing attenuation (Andersen et al., 2008b) (Table 5-44). A wide range of correlations was reported for UFP concentrations with NO_2 and CO (r = 0.33–0.69 NO_2, 0.07–0.69 CO), and the magnitude of correlation does not relate to the copollutant model results.

5.5.6 Respiratory Effects in Healthy Populations

Evidence for a relationship between short-term exposure to UFP and respiratory effects in healthy populations was very limited in the 2009 PM ISA (U.S. EPA, 2009). Epidemiologic studies found an association with wheeze in infants. Controlled human exposure studies found inconsistent evidence for decrements in lung function or pulmonary inflammation following short-term UFP exposure. Animal toxicological studies focused on exposure to mixtures such as woodsmoke and motor vehicle emissions and did not distinguish between the effects of particles and gases in the mixture.

5.5.6.1 Lung Function

5.5.6.1.1 Epidemiologic Studies

While the 2009 PM ISA (U.S. EPA, 2009) did not have a delineated discussion of epidemiologic studies that examined respiratory effects in healthy populations, an association between UFPs and wheeze was reported in a study of infants (Andersen et al., 2008a), in whom wheeze is common and transient. Several recent studies have employed scripted exposures to further inform the relationship between UFPs and respiratory effects in healthy populations. Scripted studies measuring personal ambient UFP exposures are designed to minimize uncertainty in the UFP exposure metric by always measuring UFPs at the site of exposure, ensuring exposure to sources of UFPs, such as traffic, and measuring outcomes at well-defined lags after exposure. A limitation of recent scripted exposure studies is that outcome assessment is only performed up to 6 hours after exposure, such that scripted studies do not inform understanding of the persistence of effects. There are recent epidemiologic studies in populations that include a mix of healthy participants and participants with pre-existing respiratory and/or cardiovascular disease, some of which indicate UFP-associated increases in respiratory effects. However, these studies are not evaluated in this section, as it is not known whether the results apply to the healthy portion of the population or are instead driven solely by an association in individuals with pre-existing respiratory conditions.

Respiratory effects were evaluated in recent panel studies of scripted exposures in high or low traffic areas, commute routes, or participants assigned to spend time at varying distance to a steel plant., Exposures ranged from 1 to 8 hours and the nature of exposure varied among the traffic studies, including cycling on roadways (Weichenthal et al., 2011; Zuurbier et al., 2011b), riding in a car or bus on roadways (Zuurbier et al., 2011b), and exercising near high and low traffic areas on stationary bicycles (Matt et al., 2016; Kubesch et al., 2015; Steenhof et al., 2013; Strak et al., 2012). In addition to traffic studies, Dales et al. (2013) randomly assigned participants to spend alternating weeks in a neighborhood within 1 km of a steel plant, and at a neighboring college campus, 4.5 km from the plant. In addition to varying study designs, UFP concentration metrics also varied across studies. Most studies examined NC, with a few specifying sampling in the 10−1,000 nm range (Matt et al., 2016; Kubesch et al., 2015; Dales et al., 2013).

In recent studies, increases in personal ambient UFP exposure were inconsistently associated with decreases in lung function and increases in markers of pulmonary inflammation in healthy adults in recent studies. Some studies provided evidence of transient respiratory effects associated with UFP exposure. Strak et al. (2012) reported decreases in FVC and FEV_1, and increases in eNO immediately after exposure, but not 6 or 18 hours later. Similarly, Matt et al. (2016) observed UFP-related FEV_1 decrements immediately after exposure that were positive 7-hour post exposure. Other studies observed associations with several lung function metrics, including FEV_1, FEV_1/FVC, $FEF_{25-75\%}$, total lung capacity (TLC), and residual volume (RV) (Dales et al., 2013) immediately after exposure, and PEF 2 and 6 hours after exposure (Zuurbier et al., 2011b). Notably, many studies that reported some evidence of associations had inconsistent results across an array of lung function metrics (Matt et al., 2016; Strak et al., 2012; Zuurbier et al., 2011b). Similarly, some studies reported UFP associations with lung function and eNO, but not other subclinical pulmonary effects, including nasal lavage levels of the proinflammatory cytokine IL-6 (Steenhof et al., 2013; Strak et al., 2012) or plasma CC16 levels (Zuurbier et al., 2011a), an indicator of decreased lung epithelial barrier function. Additional studies did not observe any associations between UFP concentrations and lung function or pulmonary inflammation in healthy populations up to 7 hours after exposure (Kubesch et al., 2015; Weichenthal et al., 2011; Strak et al., 2010). While respiratory symptoms are frequently studied in populations with pre-existing respiratory conditions, such as asthma or COPD, the outcome is less often examined in healthy populations. As such, no recent studies of UFP exposure evaluate respiratory symptoms or medication use in healthy populations.

In addition to major uncertainties regarding the spatial variability in UFP and the various size fractions and concentration metrics used as UFP exposure surrogates, the ability to attribute inconsistently observed associations to UFP exposure in the presence of moderately-to-highly correlated traffic-related copollutants ($r = 0.50–0.70$) remains limited. Only Strak et al. (2012) examined models with these copollutants. The authors reported that UFP associations observed immediately after exposure persisted in copollutant models including EC, Fe, Cu, NO_2, or NO_X, but results may be unreliable for models with moderately-to-highly correlated pollutants.

5.5.6.1.2 Controlled Human Exposure Studies

The 2009 PM ISA (U.S. EPA, 2009) reported evidence of small decrements in lung function following short-term UFP CAPs exposure in healthy humans in one study (Gong et al., 2008) but not another (Samet et al., 2009). In contrast, an increase in BALF IL-8 was found in Samet et al. (2009), but no evidence of pulmonary inflammation was found in Gong et al. (2008).

5.5.6.1.3 Animal Toxicological Studies

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term exposure to UFP on pulmonary function. Animal toxicological studies investigating the effects of short-term exposure to UFP-containing mixtures on subclinical effects did not distinguish between effects due to particles or gases in the mixture.

Two recent studies examined this endpoint. In one study, Sprague Dawley rats were exposed for 6 hours to filtered and unfiltered GE (count median diameter of 15−20 nm, mass median diameter of approximately 150 nm) (Seagrave et al., 2008). Neither filtered nor unfiltered GE exposure caused any change in breathing frequency, tidal volume, minute volume, or Penh. In the other study, Amatullah et al. (2012) found that a 4-hour exposure of BALB/c mice to Toronto near-UFP CAPs had no effect on pulmonary function. Additional study details for these and other recent animal toxicological studies are found in Table 5-45.

Table 5-45 Study-specific details from animal toxicological studies of short-term exposure to UFP and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	UFP CAPs Mexico City Particle size: (UF) Ultrafine $PM_{0.2}$ Control: Filtered air	Route: Inhalation Dose/Concentration: Ultrafine $PM_{0.2}$ 107 µg/m^3 Duration: Acute 5 h/day, 3 days Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of kallikrein-kinin endocrine system and RAS • Heme oxygenase-1
Cheng et al. (2016) Species: Mouse Strain: C57Bl/6J Sex: Male Age: 3 mo	Re-aerosolized collected ambient PM near a Los Angeles freeway Particle sizes: Ultrafine PM < 180 nm, median 60.6 nm Control: Reaerosolized extracts of sham filters	Route: Whole-body inhalation Dose/concentration: 343 µg/m^3 Duration of exposure: 5 h/day, 3 days/week for 5, 20 and 45 h over 3 weeks	Immunohistochemistry of nasal epithelium and brain tissue • Oxidative stress markers • Macrophage activation marker
Seagrave et al. (2008) Species: Rat Strain: Sprague-Darley Sex: Male Age/Weight: 8–10 weeks, 250–300 g	Gasoline engine exhaust (GE) Filtered GE Particle Size: GE MMD 150 nm	Route: Whole-body inhalation Dose/Concentration: GE filtered 2.4 µg/m^3 GE 59 µg/m^3 Duration of exposure: 6 h Coexposure: Combustion vapors	Pulmonary function • Breathing frequency • Tidal volume • Minute volume • Penh
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6–8 weeks	Motor vehicle exhaust (DE and GE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m^3 Duration: 6 h	BALF cells and cytokines Particle uptake in bronchial macrophages

ApoE = apolipoprotein E; DE = diesel exhaust; GE = gasoline exhaust; MMD = mass median diameter; Penh = enhanced pause.

Pulmonary Oxidative Stress

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term UFP exposure on pulmonary oxidative stress. Two recent studies examined this endpoint. Seagrave et al. (2008) exposed rats to GE (count median diameter 15–20 nm, mass median diameter 150 nm) and found increased lung tissue chemiluminescence that was not present when GE was filtered, indicating that the particulate fraction had a role in the oxidative stress response. Recently,

oxidative stress in olfactory epithelium, as well as olfactory bulb and other brain regions, was examined in mice exposed to resuspended urban UFP (Cheng et al., 2016) (see Section 8.5.2). A single 5-hour exposure to UFP resulted in enhanced markers of oxidative stress in olfactory epithelium, but not olfactory bulb, cerebellum, or cerebral cortex. Multiple exposures over 3 weeks also increased oxidative stress markers in olfactory epithelium, as well as decreased levels of a protein expressed by olfactory sensory nerves, and increased levels of apoptosis-related proteins.

Pulmonary Inflammation

The 2009 PM ISA (U.S. EPA, 2009) did not report any animal toxicological studies investigating the effects of short-term UFP exposure on pulmonary inflammation. Several recent studies examined this endpoint. No effects were observed in terms of BALF inflammatory cells in response to a 4-hour exposure of BALB/c mice to Toronto UFP CAPs (Amatullah et al., 2012) or in response to a 6-hour exposure of C57BL/6 mice to UFP generated from motor vehicle exhaust (Tyler et al., 2016), despite effects observed in the hippocampus of the latter study (see Section 8.5.2). However, inflammation was observed in two other studies measuring effects in lung tissue. Cheng et al. (2016) found inflammatory responses in olfactory epithelium, as well as olfactory bulb and other brain regions, in C57BL/6J mice exposed to resuspended urban UFP (Section 8.5.2). The number of Iba1 positive-macrophages, an indicator of inflammation, increased in olfactory epithelial turbinates and in the olfactory bulb after 5-hours of exposure to UFP ($p < 0.05$). In addition, Aztatzi-Aguilar et al. (2015) found increased levels of IL-6 in lung tissue in Sprague Dawley rats exposed to UFP CAPs in Mexico City for several days ($p < 0.05$). Aztatzi-Aguilar et al. (2015) also found that short-term UFP CAPs exposure had several effects on the two counterbalancing endocrine systems—the RAS and the kallikrein-kinin system in the lung ($p < 0.05$). These effects included upregulation of genes encoding angiotensin 1 receptor and angiotensin converting enzyme and reduced levels of reduced angiotensin 1 receptor protein. Levels of angiotensin converting enzyme protein and angiotensin 2 receptor mRNA were not impacted. The RAS plays an important role in pulmonary and systemic vasculature, with binding of angiotensin to the angiotensin 1 receptor mediating vasoconstriction and oxidative stress. In addition, short-term UFP CAPs exposure resulted in upregulation of the gene encoding kallikrein-1 ($p < 0.05$). Kallikrein-1 is a serine protease enzyme required to produce kinin peptides, which are necessary to activate bradykinin receptors. Bradykinin receptors are involved in the regulation of nitric oxide which mediates vasodilation.

5.5.6.2 Summary of Respiratory Effects in Healthy Populations

Evidence linking short-term UFP exposure and respiratory effects in healthy populations is inconsistent or minimal in epidemiologic studies and controlled human exposure studies. Animal toxicological studies found pulmonary oxidative stress following short-term UFP exposure, but inconsistent evidence of pulmonary inflammation and no evidence of changes in lung function.

5.5.7 Respiratory Effects in Populations with Cardiovascular Disease

As described in the 2009 PM ISA (U.S. EPA, 2009), Kooter et al. (2006) found that a multiday exposure of SH rats to UFP-enriched CAPs in the Netherlands decreased CC16 in BALF. CC16 is a secretory product of nonciliated bronchiolar Club cells and is thought to contribute to control of inflammation. Recently, Tyler et al. (2016) exposed C57BL/7 and ApoE knockout mice for 6-hour to UFP generated from motor vehicle exhaust. No increases in BALF inflammatory cells were observed. However, increases in TNF-α levels in BALF and particle uptake into bronchial macrophages were found in ApoE knockout ($p < 0.001$) but not in C57BL/6 mice. Effects were also seen in the hippocampus (Section 8.5.2). Additional study details are presented in Table 5-45.

5.5.8 Respiratory Mortality

In the 2009 PM ISA (U.S. EPA, 2009), no studies specifically examined associations between short-term UFP exposure and respiratory mortality. Although recent studies examine the relationship between short-term UFP exposure and respiratory mortality, the total body of evidence remains small, as detailed in CHAPTER 11 (Section 11.4.1). Across studies that examined the UFP—respiratory mortality relationship, there is inconsistency in the particle size distribution that was used to represent UFP exposures with some studies measuring NC, while other studies measured NC with the upper end of the size distribution ranging from 100—3,000 nm. This disparity in the measurement of UFPs between studies complicates the overall interpretation of results.

The assessment of the relationship between short-term UFP exposure and respiratory mortality is limited to studies conducted in Europe (Stafoggia et al., 2017; Lanzinger et al., 2016a; Samoli et al., 2016b) and China (Leitte et al., 2012). Across studies of respiratory mortality, NC was used to examine associations with respiratory mortality. Both Lanzinger et al. (2016a), in a study of five central European cities as part of the UFIREG project, and Leitte et al. (2012), in Beijing, China, reported generally positive associations that were imprecise across each of the UFP size distributions examined (Table 11-9, UFP studies in mortality chapter), while Samoli et al. (2016b) did not report any evidence of an association with respiratory mortality. Although there is some evidence of a positive association between short-term UFP exposure and respiratory mortality, within each study only a single monitor was used to estimate exposure to UFPs (Table 11-9, UFP studies in mortality chapter). As detailed in CHAPTER 2 (Section 2.5.1.1.5, Section 2.5.1.2.4, and Section 2.5.2.2.3), the use of a single monitor does not adequately account for the spatial and temporal variability in UFP concentrations as well as the change in the particle size distribution that changes with distance from source.

5.5.9 Summary and Causality Determination

A limited number of studies examining short-term exposure to UFPs and respiratory effects were reported in the 2009 PM ISA (U.S. EPA, 2009), which concluded that the relationship between short-term exposure to UFP and respiratory effects is "suggestive of a causal relationship". This conclusion was based on epidemiologic evidence indicating associations with combined respiratory-related diseases, respiratory infection, and asthma exacerbation. In addition, personal ambient UFP exposure from time spent in high- and low-traffic areas were associated with lung function decrements in adults with asthma. The few available experimental studies provided limited coherence with epidemiologic findings for asthma exacerbation. Recent studies add to this evidence base and support epidemiologic evidence for asthma exacerbation and combined respiratory-related diseases but do not rule out chance, confounding, and other biases. Several animal toxicological studies showing effects related to allergic asthma provide biological plausibility. The evidence characterizing the relationship between short-term exposure to UFP and effects on the respiratory is detailed below (Table 5-46), using the framework for causality determinations described in the Preamble to the ISAs (U.S. EPA, 2015).

For asthma exacerbation, there is some epidemiologic evidence that is not entirely consistent. Associations persisted in one epidemiologic study with adjustment for NO_2, but not in another. Additional supporting evidence, showing decrements in lung function and enhancement of allergic inflammation and other allergic responses, is provided by a controlled human exposure study in adults with asthma and by animal toxicological studies in an animal model of allergic airway disease. For combined respiratory-related diseases, recent findings add consistency for hospital admissions and ED visits and indicate lung function changes among adults with asthma or COPD. Uncertainty remains regarding the representativeness of UFP concentrations as a surrogate for exposure and for copollutant confounding, which limits inference about an independent effect of UFP. Additionally, there remains limited information on the spatial and temporal variability of UFP concentrations (Section 2.4.3.1). **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and respiratory effects.**

Table 5-46 Summary of evidence for that is suggestive of, but not sufficient to infer, a causal relationship between short-term UFP exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Asthma exacerbation and combined respiratory-related diseases			
Evidence from multiple, high quality epidemiology studies at relevant UFP concentrations is generally consistent, but limited	Increases in asthma-related hospital admissions, ED visits, and physician visits in children and all ages combined.	Samoli et al. (2016a) Iskandar et al. (2012) Evans et al. (2014)	
	Increases in combined respiratory-related diseases observed in single-city and multicity studies.	Section 5.5.5	
Uncertainty regarding confounding by copollutants	Potential copollutant confounding for asthma-related hospital admissions and lung function is examined in a few studies, with some evidence that associations remain robust in models with gaseous pollutants.	Andersen et al. (2008b) McCreanor et al. (2007) Samoli et al. (2016a) Halonen et al. (2009b)	
Limited coherence in epidemiologic studies across the continuum of effects	Increases in respiratory symptoms, pulmonary inflammation and lung function decrements observed in a limited number of panel studies in adults with asthma provide limited support for asthma exacerbation in children.	Mar et al. (2004) von Klot et al. (2002) McCreanor et al. (2007) Mirabelli et al. (2015)	
Uncertainty regarding exposure measurement error	Most studies relied on one monitor to measure UFPs, which is inadequate based on limited data demonstrating both that there is greater spatial variability in UFPs (i.e., NC) and that the particle size distribution changes with distance from source. Additionally, there is limited information on the temporal variability in UFP concentrations.	Section 2.4.3.1	
Uncertainty regarding exposure metric and UFP size fraction	Inconsistency in the UFP metric used (i.e., NC, SC, and MC) and UFP size fraction examined complicating interpretation of results across studies.	Table 5-40 Table 5-42 Table 5-43 Table 5-44 Section 5.5.8	

Table 5-46 (Continued): Summary of evidence for that is suggestive of, but not sufficient to infer, a causal relationship between short term ultrafine particle (UFP) exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Limited evidence from controlled human exposure studies	In adults with asthma, decreases in pulmonary function are observed.	Gong et al. (2008)	100 μg/m^3
Limited evidence from toxicological studies at relevant concentrations	Enhancement of allergic inflammation and other allergic responses is observed in animal model of allergic airway disease.	Section 5.5.2.3 Li et al. (2009)	101 μg/m^3
Biological plausibility for allergic asthma	Evidence from animal toxicological studies provides biological plausibility for epidemiologic findings of allergic asthma, the most common phenotype in children.	Section 5.5.1 Section 5.5.2.3	
Respiratory effects in healthy populations			
Some evidence from toxicological studies at relevant concentrations	Pulmonary function was not affected. Inconsistent results were found for pulmonary inflammation, while some evidence was found for oxidative stress and changes in the RAS.	Section 5.5.6.1.3	59–793 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

5.6 Long-Term UFP Exposure and Respiratory Effects

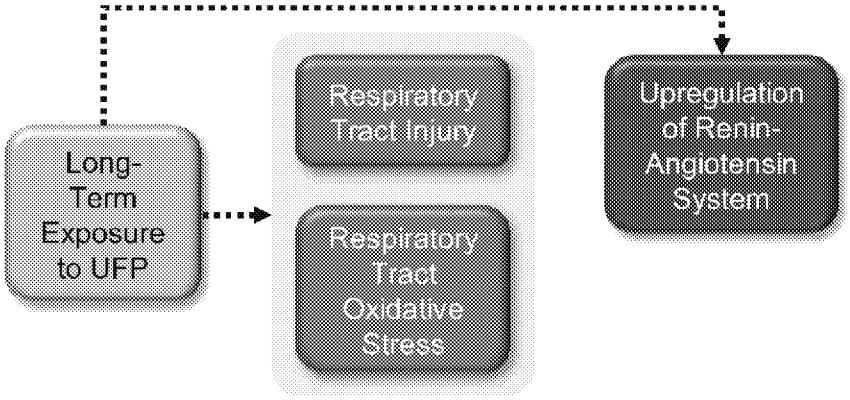
The 2009 PM ISA concluded that the evidence was inadequate to assess the relationship between long-term exposure to UFP and respiratory effects (U.S. EPA, 2009). At that time, there were no epidemiologic studies available to address this relationship. Animal toxicological studies found that long-term exposure to UFP CAPs had no effect, while long-term exposure to GE and DE altered respiratory-related endpoints. Studies with DE did not determine whether the effects were due to the particulate or gaseous part of the mixture. However, the effects of the GE were attributable to particulate matter. Recent studies consist of one epidemiologic study that examines the association between long-term exposure to UFP and respiratory outcomes and a small number of recent animal toxicological studies that provide evidence for respiratory effects.

5.6.1 Biological Plausibility

Due to a paucity of data, it is not possible to describe biological pathways that potentially underlie respiratory effects resulting from long-term exposure to UFP. Figure 5-50 graphically depicts the upstream events that may lead to downstream events observed in the single epidemiologic study. This discussion of "how" long-term exposure to UFP may lead to respiratory effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 5.6.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see CHAPTER 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential." Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see CHAPTER 4). Immune system responses due to the presence of particles in the interstitial space may contribute to respiratory health effects.

Although all size fractions of PM may contribute to oxidative stress, UFPs may contribute disproportionately more as a function of their mass due to their large surface/volume ratio. The relative enrichment of redox active surface components, such as metals and organics, per unit mass may translate to a relatively greater oxidative potential of UFPs compared with larger particles with similar surface components. In addition, the greater surface per unit volume may deliver relatively more adsorbed soluble components to cells. These components may undergo intra-cellular redox cycling following cellular uptake. Furthermore, per unit mass, UFPs may have more opportunity to interact with cell surfaces due to their greater surface area and their greater particle number compared with larger PM. These interactions with cell surfaces may lead to ROS generation, as described in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). Recent studies have also demonstrated that UFPs have the capacity to cross cellular membranes by nonendocytotic mechanisms involving adhesive interactions and diffusion, as described in CHAPTER 4. This may allow UFPs to interact with or penetrate intra-cellular organelles.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 5-50 Potential biological pathways for respiratory effects following long-term UFP exposure.

Evidence that long-term exposure to UFP may affect the respiratory tract is provided by a limited number of experimental studies. While markers of injury and oxidative stress were increased (Zhang et al., 2012; Reed et al., 2008), no inflammatory changes were observed (Tyler et al., 2016; Aztatzi-Aguilar et al., 2015; Araujo et al., 2008; Reed et al., 2008). In Tanaka et al. (2013a), the enhancement of allergic responses seen following long-term exposure to UFP-enriched DE was not attributable to particulate components, suggesting a role for combustion gases in mediating the response. Similarly, the presence of 8-OH deoxy-guanosine observed in lung tissue was likely due to combustion gases. Upregulation of the RAS, as indicated by an increase in mRNA and protein levels of angiotensin receptor Type 1, was observed in the lung (Aztatzi-Aguilar et al., 2015). Angiotensin receptor Type 1 mediates the effects of angiotensin II, which is a potent vasoconstrictor and mediator in the vasculature. The SNS and the RAS are known to interact in a positive feedback fashion (Section 8.1.2) with important ramifications in the cardiovascular system. However, it is not known whether SNS activation or some other mechanism mediated the changes in the RAS observed in the respiratory tract in this study. The upstream events presented here may provide biological plausibility for epidemiologic evidence of respiratory health effects and will be used to inform a causality determination, which is discussed later in the chapter (Section 5.4.9).

5.6.2 Development of Asthma

The 2009 PM ISA (U.S. EPA, 2009) did not report any studies evaluating allergic responses resulting from long-term exposure to UFP. Recently, Tanaka et al. (2013a) evaluated the enhancement of allergic responses by exposure to UFP-enriched DE. ICR mice were exposed to two concentrations of diluted DE and to particle-depleted diesel exhaust (0DE) for 8 weeks. Concentrations of gaseous components of DE were similar in the high DE and 0DE atmospheres (3.3 ppm CO, 1.4 ppm NO_X, and 0.51 ppm NO_2), but the low DE had approximately 1/3 of these concentrations (1.2, 0.41, and 0.15, respectively). Mice were sensitized and challenged with OVA administered by intra-tracheal instillation during the 8-week inhalation exposure. Mice exposed to filtered air and OVA had a modest increase in airway eosinophils that was enhanced by exposure to low and high DE in a dose-dependent fashion ($p < 0.05$ compared with OVA controls). This response was not dependent on the particulate part of the aerosol, since numbers of eosinophils in allergic animals exposed to 0DE, which was depleted of particles, were similar in the high DE group. Furthermore, increases in IL-5, IL-13, eotaxin, and myeloperoxidase protein in lung tissue reached similar levels in allergic mice exposed to either high DE or 0DE ($p < 0.05$ compared with OVA controls). Interestingly, only the allergic mice exposed to the particle-depleted 0DE had increases in lung tissue IL-4, IL-17α, IL-1β, lipid peroxidase, and serum IgE ($p < 0.05$ compared with OVA controls). Results from this study indicate a critical role for the combustion gases in DE-associated enhancement of allergic responses. Companion studies also detected the presence of 8-OH deoxy-guanosine in lung tissue in high DE and particle-depleted 0DE allergic mice (Tanaka et al., 2013b). Additional study details are found in Table 5-47.

Table 5-47 Study-specific details from animal toxicological studies of long-term UFP exposure and allergic responses.

Study/Study Population	Pollutant	Exposure	Endpoints
Tanaka et al. (2013a) Species: Mouse Sex: Female Strain: ICR Age/Weight: 6 weeks	Diesel engine exhaust Low DE = 36 μg/m^3 High DE = 169 μg/m^3 Particle size: 26–27 nm in low and high DE	Route: Whole-body inhalation Dose/Concentration: 5 h/day, 5 days/week for 8 weeks OVA intra-tracheal every other week (5 total) Time to analysis: 24 h after last instillation	BALF cells BALF cytokines Serum IgE
Tanaka et al. (2013b) Species: Mouse Sex: Female Strain: ICR Age/Weight: 6 weeks	Diesel engine exhaust Low DE = 36 μg/m^3 High DE = 169 μg/m^3 Particle size: 26–27 nm in low and high DE	Route: Whole-body inhalation Dose/Concentration: 5 h/day, 5 days/week for 8 weeks OVA intra-tracheal every other week (5 total) Time to analysis: 24 h after last instillation	Oxidative stress • -Lung 8-OH deoxy guanosine levels

BALF = bronchoalveolar lavage fluid; DE = diesel exhaust; IgE = Immunoglobulin E; OVA = ovalbumin.

5.6.3 Subclinical Effects in Healthy Populations and Populations with Cardiovascular Disease

Animal toxicological studies provide evidence for subclinical effects potentially underlying the development of respiratory disease in healthy populations and in populations with cardiovascular disease. The 2009 PM ISA (U.S. EPA, 2009) reported several studies that evaluated the effects of long-term exposure to UFP on subclinical effects. Reed et al. (2008) exposed F344 rats for 6 months to GE containing UFP (count median diameter 15–20 nm, MMD 150 nm). LDH was increased in BALF of rats, but no inflammatory or histopathologic changes were found except for the accumulation of PM-containing macrophages. However, hypermethylation of lung DNA was observed. The significance of DNA methylation in terms of respiratory health is unclear, although it is known that altered patterns of DNA methylation can affect gene expression and are sometimes associated with altered immune responses and/or the development of cancer. The LDH and hypermethylation responses were prevented by addition of a particle filter, indicating that the particulate portion of the GE mixture played a role in the response. In a study in ApoE knockout mice exposed to UFP CAPs for 40 days, Araujo et al. (2008) found no increase in BALF inflammatory cells exposed to UFP CAPs for 40 days.

Several recent studies have become available since the 2009 PM ISA that examine the effects of long-term UFP exposure on pulmonary oxidative stress and inflammation. Zhang et al. (2012) collected ambient UFP near a Los Angeles freeway. Exposure of C57BL/6J mice to the reaerosolized UFP for

10 weeks resulted in increases in mRNA and protein levels of heme oxygenase-1, NADPH quinone oxidoreductase 1, γ-glutamyl cysteine ligase catalytic subunit, and γ-glutamyl cysteine synthetase modifier subunit in the lung ($p < 0.05$). These are Phase II regulated detoxifying enzymes and are important in defense against oxidative stress. Young mice (3 months) had a more robust increase in gene expression and protein levels than older mice (18 months). Zhang et al. (2012) also found evidence of upregulation of Phase II enzymes in specific brain regions (Section 8.6.3) and the liver. In contrast, Aztatzi-Aguilar et al. (2015) found decreased lung tissue heme oxygenase-1 activity in Sprague-Dawley rats following 8-weeks exposure to Mexico City UFP CAPs ($p < 0.05$) and no change in γ-glutamyl cysteine ligase catalytic subunit was observed. Aztatzi-Aguilar et al. (2015) also found decreased protein levels of IL-6 in lung tissue ($p < 0.05$). Further, Tyler et al. (2016) exposed C57BL/7 and ApoE-knockout mice to UFP generated from motor vehicle exhaust. A 30-day exposure resulted in no increase in inflammatory cells or cytokines in the BALF. Particle uptake into bronchial macrophages was increased in both C57BL/6 and ApoE knockout mice ($p < 0.05$). Effects were also seen in the hippocampus (Section 8.6.3). Aztatzi-Aguilar et al. (2015) found that long-term UFP CAPs exposure had several effects on the RAS, including induced lung expression of the angiotensin 1 receptor gene, and increased angiotensin 1 receptor protein levels ($p < 0.05$). Protein levels and mRNA of angiotensin converting enzyme were not impacted. Components of the RAS play an important role in the pulmonary circulation. Overall, older and recent studies provide some limited evidence for pulmonary injury, DNA hypermethylation, and changes in the RAS, inconsistent evidence for pulmonary oxidative stress and no evidence for pulmonary inflammation. Additional study details for these recent animal toxicological studies are found in Table 5-48.

Table 5-48 Study-specific details from animal toxicological studies of long-term UFP exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Aztatzi-Aguilar et al. (2015) Species: Rat Sex: Male Strain: Sprague Dawley	UFP CAPs Mexico City Particle size: Ultrafine $PM_{0.2}$ Control: Filtered air	Route: Inhalation Dose/Concentration: Ultrafine $PM_{0.2}$ 107 µg/m^3 Duration: Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene and protein expression in lung tissue • IL-6 • Components of kallikrein-kinin endocrine system and RAS • Heme oxygenase-1
Reed et al. (2008) Species: Rat Sex: Male and Female Strain: F344 Age/Weight:	DE and filtered DE Particle size: MMAD 150 nm	Route: Whole-body Inhalation Dose/Concentration: 3 concentrations, H 59 µg/m^3, M 30 µg/m^3, L 6.6 µg/m^3, high filtered 2 µg/m^3 Duration: 6 h/day for 7 days/week, 3 days (1 week), 6 mo Coexposure: Combustion products	Lung Injury • -BALF LDH Lung DNA Alteration—Hypermethylation
Tyler et al. (2016) Species: Mouse Strain: C57BL/6 and ApoE knockout Age/Weight: 6–8 weeks	Motor vehicle exhaust (DE and GE) passed through a denuder to generate UFP Particle size: 147.1 nm ± 1.3 nm Control: Filtered air	Route: Whole-body inhalation Dose/Concentration: 371.3 ± 15.6 µg/m^3 Duration: 6 h/day for 30 days	BALF cells and cytokines Particle uptake in bronchial macrophages
Zhang et al. (2012) Species: Mouse Strain: C57BL/6J Sex: Male Age: 3 mo, 18 mo	Reaerosolized collected ambient PM near a freeway Particle size: Ultrafine PM < 200 nm	Route: Whole-body inhalation Dose/concentration: 200–400 ug/m^3 Duration of exposure: 5 h/day, 3 days/week for 10 weeks	Oxidative Stress Markers—Lung GCLC and GCLM mRNA and protein

ApoE = apolipoprotein E; BALF = bronchoalveolar lavage fluid; DNA = deoxyribonucleic acid; DE = diesel exhaust; GCLC = glutamate cysteine ligase catalytic subunit; GCLM = glutamate cysteine ligase modifier subunit; H = high; IL-6 = interleukin 6; L = low; M = medium; MMAD = mass median aerodynamic diameter; LDH = lactate dehydrogenase; Mrna = messenger ribonucleic acid; RAS = renin-angiotensin system.

5.6.4 Respiratory Mortality

Overall, the literature base for long-term UFP exposure and respiratory mortality remains very small, with one study (Ostro et al., 2015) reporting results for UFP mass concentration. The authors examined the association between UFP (<0.1 µm) mass concentrations and respiratory mortality among

women in the California Teachers Cohort using a CTM to predict UFP concentrations with a 4-km spatial resolution and observed an association near the null value.

5.6.5 Summary and Causality Determination

Based on limited evidence from animal toxicological studies and a lack of epidemiologic studies, the 2009 PM ISA (U.S. EPA, 2009) concluded that evidence was inadequate to assess the relationship between long-term exposure to UFP and respiratory effects. Since then, only a few new studies have become available. The evidence characterizing the relationship between long-term exposure to $PM_{10-2.5}$ and respiratory effects is detailed below (Table 5-49), using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015). Currently, there is limited epidemiologic evidence for respiratory mortality. But uncertainty regarding copollutant confounding and exposure measurement error results in an inability to rule out chance and confounding. A few animal toxicological studies provide evidence of effects resulting from long-term exposure to UFP. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and respiratory effects.**

Table 5-49 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and respiratory effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Limited epidemiologic evidence does not support a relationship	No association was observed with UFP mass concentrations in a single study of respiratory mortality from the California Teachers Study cohort.	Ostro et al. (2015)	UF mass concentration: 1.29
Uncertainty regarding confounding by copollutants and exposure measurement error	Uncertainties are not addressed.	Ostro et al. (2015)	
Some evidence for respiratory effects from toxicological studies at relevant concentrations	Results show injury, oxidative stress, DNA hypermethylation, and changes in the RAS, but no pulmonary inflammation.	Section 0	59–400 μg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

bDescribes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations and metric (i.e., number concentration [NC], surface area concentration [SC], mass concentration [MC]) with which the evidence is substantiated.

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